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Anabolic treatment of osteoporosis

Sosa Henríquez M[1,2], Rosa F de la[1], Suárez N[1]
1 University of Las Palmas de Gran Canaria. Biomedical and Health Research University Institute. Osteoporosis and Mineral Metabolism Research Team. Las Palmas de Gran Canaria (Spain)
2 Insular University Hospital. Bone Metabolism Unit. Las Palmas de Gran Canaria (Spain)

Summary
The anabolic or osteogenic treatment constitutes one of the pillars in the treatment of osteoporosis as it makes it possible to build new bone and improve the bone microstructure. Over the years, several drugs classified as osteogenic agents have emerged, but some of them have not been effective while the use of others has been discontinued. Nowadays we only have one anabolic drug, the teriparatide, which, despite the time that passed since its approval, has established itself as the anabolic drug of reference.
There are many studies about the usefulness of teriparatide when administered alone, or in combination with antiresorptive drugs, or sequentially, where the order for the drugs administration appears to be important.
We analyze all these sections and make some final recommendations about its use in accordance with the currently available clinical practice guidelines.

Key words: teriparatide, osteogenic, anabolic.

Anabolic discontinued or not available

Sodium fluoride

Sodium fluoride (FNa) was used in the past as a bone-forming drug. Administering fluoride causes the number of osteoblasts to increase as the proliferation of osteoblastic precursors is stimulated, which leads to increased activity. In addition, it has antiresorptive capacity. The combination of osteogenic effect and inhibition of bone resorption leads to an increase in bone mineral density (BMD)[1].

Although the number of randomized clinical trials conducted with FNa is relatively limited, the salt types and dosages used in them, as well as their combination with calcium and vitamin D, make every trial very different from each other and therefore the global assessment of the results turns very difficult.

There are some studies that have shown an increase in BMD and a reduction in the risk of vertebral fractures, but in general the published results have been disappointing. Despite almost uniformly observing a statistically significant increase of BMD, these studies do not record a reduction in the risk of fractures[2]. Moreover, sometimes they instead record an even higher risk of suffering fractures during treatment or when suspending it, especially of non-vertebral nature[3].

One of these studies was the study by Riggs et al.[4], published in the prestigious New England Journal of Medicine. The study showed very poor results, causing the FNa not to be approved by the Food and Drug Administration (FDA). This well-designed, double-blind study included 202 postmenopausal women at an average age of 68 years. All patients received a calcium supplement (1,500 mg/day), while the experimental group also received 75 mg/day of FlNa. The patients' BMD in the experimental group significantly increased by 35% in the lumbar spine and 12% in the head of the femur if compared to the control group patients' BMD, while a significant decrease of 4% was also noticed in the radius. Although the number of vertebral fractures was similar in the 2 groups during the next 4-year follow-up, the number of non-vertebral fractures was higher in the experimental group.

Subsequently, a Cochrane review, including 11 studies with a total of 1,429 patients, concluded that although FNa can increase the BMD of the lumbar spine, no reduction in vertebral fractures is observed. By increasing the fluoride dosage, the risk of non-vertebral fractures and gastrointestinal side effects increase, not showing any beneficial effect on the rate of vertebral fractures[5].

For these reasons, FNa was never approved by health authorities around the world and no results from new trials have been published in the past 20 years. So, its use for treating osteoporosis has been discontinued.

Intact parathyroid hormone (PTH 1-84)

The intact parathyroid hormone molecule (PTH 1-84) was been used in the treatment of osteoporosis in the past decade.

An initial study, published in 2003, showed an increase in BMD in the experimental group treated with PTH 1-84[6] and became a reference in reducing the risk of fractures and thus demonstrating its usefulness for the treatment of postmenopausal osteoporosis, was publis-

Correspondence: Manuel Sosa Henríquez (manuel.sosa@ulpgc.es)

hed by Greenspan et al. in 2007[7]. The randomized, double-blind, placebo-control study was conducted on 2,532 postmenopausal women and showed that patients who received PTH 1-84 had a significant increase in BMD in the lumbar spine and in the proximal femur (femoral neck, total hip and trochanter) and a decrease in the BMD of the distal radius. A statistically significant reduction in the risk of suffering new fragility fractures was observed, but only regarding vertebral fractures, but not so regarding non-vertebral fractures. The dropout rate was significant and up to 95% of the patients suffered some type of side effects. Although several studies on PTH 1-84 have been published[8-12], some on the combination with other antiresorptive drugs, none of them showed a reduction in the risk of non-vertebral or hip fractures. Perhaps, the drug was never approved by the FDA to be used in the US for this very reason, and although it was approved in Europe, the manufacturing lab suddenly suspended its supply shortly after and to this day, not even with a prescription it can be obtained. Lately it has returned to the news for its possible usefulness in the treatment of hypoparathyroidism.

Abaloparatide

Abaloparatide is a synthetic peptide analogue to the PTH-like protein (PTH-RP 1-34) that selectively binds to the cellular receptors for PTH/PTH-RP[13], increasing BMD at both vertebral and cortical bone levels[14]. A study carried out including approximately 2,400 women who were administered abaloparatide to compare it to teriparatide, showed a relative risk reduction in the appearance of new morphometric vertebral fractures, with no statistically significant differences between both drugs[15.] Abaloparatide also reduced the risk of non-vertebral fractures by 43%, but the study did not show significant differences between that and the reduction provoked by teriparatide. In all cases both, teriparatide and abaloparatide, showed differences in the reduction of the risk of statistically significant fractures compared to the placebo group[14-16].

Abaloparatide was approved for commercialization by the FDA, but the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) did not, due to an increased cardiovascular risk seen in postmenopausal women, and also owing to not reducing the risk of non-vertebral fractures in non-menopausal women.

Teriparatide

Teriparatide is a PTH analogue that contains only the first 34 amino acids, the ones promoting its biological activity. More than 15 years after its approval, it is currently the only drug approved in our country for the treatment of osteoporosis, whose mechanism of action produces the stimulation and formation of new bone[16].

Mechanism of action

Osteoblasts (the cells responsible for bone formation) have PTH receptors and its anabolic responses occur as a consequence of the hormone-receptor bindings[17]. Besides osteoblasts, osteocytes and renal tubular cells also have receptors for PTH[16]. The pharmacological efficacy of PTH requires its administration to be intermittent as bone formation is preferentially stimulated this way since prolonged or continuous administration of the hormone seems to promote bone resorption[17,18].

When sequentially administered, and as a consequence of the increase in osteoblastic activity, there is an increase in trabecular bone and an improvement in bone microarchitecture[17,19,20], showing a concomitant increase in bone cortical porosity, as well as in cortical thickness and in bone size[19,20].

Reduced risk of fracture

On the one hand, the clinical trials carried out showed an increase in BMD[21,22] as well as a reduction in the risk of vertebral and non-vertebral fractures[23-27]. The baseline study by Neer et al. was published in the New England Journal of Medicine[27]. It included 1,637 postmenopausal women with low BMD, presenting at least one prevalent fracture and who did not receive hormone replacement therapy or any other antiresorptive treatment. They were randomly grouped into 3 groups that received 20 or 40 µg/day of teriparatide or placebo. Patients who received teriparatide presented an increase in BMD of the lumbar spine of 9% with 20 µg/day, and of 13% with 40 µg/day, as well as an increase in the femoral neck of 3% with 20 µg/day, and of 6% with 40 µg/day. The BMD of the radius decreased in the 3 study groups (two groups under the effects of teriparatide and one control group), but the decrease was statistically significant in the group that received 40 µg/day in comparison with the placebo group. Compared with the placebo group, the risk of developing a new vertebral fracture decreased by 65% in the group receiving 20 µg/day and by 69% in the group receiving 40 µg/day. The risk of non-vertebral fractures decreased by 53% in the group receiving 20 µg/day and by 54% in the group receiving 40 µg/day, also compared to the placebo group[23,27]. Different studies carried out in other types of patients have obtained similar results[28-30].

In this study, no reduction in the risk of hip fracture was observed, but subsequent systematic reviews and meta-analyses have confirmed that teriparatide also reduces the risk of hip fracture[31,32].

On the other hand, several studies have shown that postmenopausal women treated with teriparatide present a decrease in ,both moderate and severe, back pain associated with vertebral fractures[28,33-35] which conditioned an improvement in their quality of life[36].

The beneficial effect of teriparatide is not affected by the age of the patients. In a study carried out in elderly women of over 75 years of age, a reduction in the risk of fracture, both vertebral and non-vertebral, was found, including those in the subgroup formed by patients older than 80 years of age[26].

Osteoporosis in men and steroid-induced osteoporosis

In addition to the initial study by Slovik et al.[37], which we could consider almost anecdotal due to the small sample size, other more methodologically complete studies have been published, allowing us to establish the usefulness of teriparatide in the treatment of osteoporosis in men.

The first study of these characteristics was the one carried out by Kurland et al. which included 23 men who received 400 units of teriparatide or placebo per day (equivalent to 25 µg/day) for 18 months. Patients who received the drug showed a 13.5% increase in BMD of the lumbar spine. The BMD of the hip also increased, but in a minor degree (2.9%) and more slowly, while the BMD in the radius did not change significantly.

In another study, conducted on 437 patients with idiopathic or hypogonadic osteoporosis, Orwoll et al. administered 20 or 40 µg/day of teriparatide to the experimental group, and calcium and vitamin D to the placebo group, obtaining an increase of 5.9% in the lumbar spine and 1.5% in the femoral neck in those treated with the drug.

Since then, several studies about men and patients receiving oral glucocorticoids have been published. On the one hand, these studies have confirmed the efficacy of teriparatide in reducing the risk of fragility fracture[37-40] and, on the other, they have confirmed the superiority of teriparatide for this task, in combination both with alendronate and risedronate[41-43]. For this reason, teriparatide is accepted for the treatment of osteoporosis in men and steroid-induced osteoporosis, in addition to postmenopausal osteoporosis.

Security. Side effects. Osteosarcoma risk

Teriparatide is well tolerated. The side effects collected from the original series of 1,943 patients by Neer et al. include nausea, headaches, and dizziness that occurred in patients who received the highest doses of the drug. Mild hypercalcaemia, defined as a serum calcium concentration greater than 10.6 mg/dl, was also observed in 2% of the women who received placebo, in 11% of the women who received 20 mg teriparatide and in 28% among those in the group that received 40 µg/day. In all cases, hypercalcemia was transient and calcium monitoring is not required in treatment with teriparatide.

When teriparatide was approved in the US for the treatment of postmenopausal osteoporosis in 2003, its use was limited to 2 years, given that a strain of rats received teriparatide at a dose proportionally higher than that subsequently used in humans developed osteosarcoma[44]. That same year, the Osteosarcoma Surveillance Study was founded in that country in order to monitor the possible appearance of osteosarcoma in patients treated with teriparatide.

During the period between January 2003 and December 2016, 3 cases of osteosarcoma were observed in patients who had received teriparatide. Based on the known incidence of osteosarcoma, the expected number of cases was 4.1 and with the 3 collected, a standardized incidence ratio of 0.72 was obtained (95% CI 0.20 to 1.86). This confirmed that the incidence of osteosarcoma associated with the use of teriparatide was not different from that observed in the general population[45].

On the other hand, no cases of osteonecrosis of the jaws have been described after using teriparatide. On the contrary, some studies have published teriparatide could have a certain beneficial effect in these patients[46-48].

What to do after 24 months of treatment with teriparatide?

Treatment with teriparatide is limited to 24 months as indicated above. Once completed, it must be suspended.

Some studies have shown that after stopping teriparatide a certain residual effect is observed[49-51]. This effect has lasted up to 24 months after stopping the drug[51] and the dreaded rebound effect has not been observed, unlike in the case of other drugs such as denosumab[52-54]. However, once the treatment with teriparatide is completed, it is advisable to continue the treatment with a bisphosphonate[55] agent and in all cases with non-pharmacological measures: exercise, a balanced diet, and a supplement of calcium and vitamin D[56-59].

Romozosumab

Romozosumab is a monoclonal antibody that has a dual effect on bone remodelling, since it inhibits sclerostin and secondarily RANKL, producing a rapid increase in bone formation that is associated with a decrease in resorption. As a consequence, it increases the trabecular and cortical bone, which translates into a significant increase in BMD and a decrease in the risk of fracture. It is indicated for the treatment of severe osteoporosis only in postmenopausal women with a high risk of fracture[60-64].

Romozosumab is given as two subcutaneous injections of 105 mg each, once a month for up to one year. The second injection should be given immediately after the first but at a different injection site. It is advisable to assess the cardiovascular risk in the patients for whom it is to be prescribed, before and during its use[65].

When to start an anabolic treatment?

Teriparatide is the only anabolic drug that currently available for treating osteoporosis in Spain. In addition to postmenopausal osteoporosis, teriparatide is approved for use in male osteoporosis and steroid-induced osteoporosis.

In our opinion, PTH is the strongest biological treatment available for osteoporosis. Both teriparatide and PTH (1-84) have been approved in our country for the treatment of postmenopausal osteoporosis. However, to correctly place it within the therapeutic arsenal, the cost of teriparatide must be taken into account, as it is currently higher than any other approved treatment for osteoporosis. Therefore, its use should be restricted to specific cases, with severe osteoporosis, such as in patients with vertebral fractures or multiple osteoporotic fractures, or with a very low BMD (T-score less than -3.5), or in those cases in which patients cannot tolerate other treatments and have a high risk of fracture[66-72]. Finally, we could also consider those cases in which there is a poor therapeutic response to other drugs, this manifesting as the appearance of recurrent fractures or a significant, documented and sustained decrease in BMD despite antiresorptive treatment. In this regard, the guidelines of the Spanish Society for Bone Research and Mineral Metabolism (SEIOMM) recommend the anabolic treatment with teriparatide precisely in these patients[55].

Sequential treatment

The treatment of osteoporosis is limited in time for several reasons. In the first place, there are drugs that have a limited administration time, such as teriparatide at two years or romozosumab at one year. Secondly, side effects or a lack of therapeutic response may appear making it necessary to change to another drug. Finally, after the time the safety of the administered drug has been established, it may be advisable to change it for a different one.

If we consider all the available drugs individually, the possible combinations are many. But by grouping them into anabolic and antiresorptive agents, we could in general lines indicate that when establishing a sequential treatment, it is advisable to start with an anabolic treatment and then continue with an antiresorptive one.

Thus, the sequential teriparatide-raloxifene treatment managed to maintain or even increase the BMD gain achieved with the previous treatment with teriparatide[73]. The same has been observed when the treatment with teriparatide is administered together with a

bisphosphonate, even producing a subsequent increase in BMD and maintaining the reduction in the risk of fracture[50]. In the case of the abaloparatide and alendronate sequence it was found that when administering this antiresorptive after the osteogenic agent, an increase in the previously achieved BMD was produced and thus preserving the anti-fracture activity[74].

On the contrary, previous treatment with a strong antiresorptive, such as alendronate or zoledronate followed by an osteogenic agent, such as teriparatide, produces a decrease in BMD in the first months after the start of the treatment[75], although the reduced risk of fracture remains[76].

If the risk of fracture in patients has been found to be high, it is advisable to start an osteogenic treatment, with a drug such as teriparatide, and then continue with a strong bisphosphonate, such as alendronate or zoledronate.

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