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Teriparatide in the treatment of postmenopausal osteoporosis

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Introduction

Nowadays there are many therapeutic options available for the treatment of osteoporosis. The objective of this treatment is to reduce the risk of fractures, both vertebral and non-vertebral. Fractures due to osteoporosis bring with them a high level of morbid-mortality¹, as well as the social and health costs they carry. In clinical trials the principal parameter for the measurement of the efficacy of treatment of osteoporosis is the reduction in risk of fracture. However, in clinical practice, a follow up after treatment is carried out with a series of measurements of bone mineral density (BMD). Although there is a clear relationship between BMD and the risk of fracture in patients without treatment, this correlation is not so clear in treated patients². This is important because it should not be forgotten that the objective of treatment for osteoporosis is the reduction in fractures independently of any modification in BMD. This, although it may be an objective parameter for evaluating the response to treatment, never should be its aim.

Among the many therapeutic options teriparatide, or human recombinant PTH (1-34), has an outstanding position. It is classified in the group of bone forming or anabolic drugs in counterpoint to those called anticatabolics or antiresorptives³. It is administered as a daily self-administered subcutaneous injection, with an easily used preloaded pen, and induces the formation of new bone, increasing the rate of bone remodelling in favour of formation, with an increase in trabecular connectivity and thickening of the cortical bone⁴. Teriparatide

improves the mechanical properties of bone⁵, giving as a result a significant reduction in vertebral and non-vertebral fractures in postmenopausal women with osteoporosis⁶, in men, and in those with corticoid osteoporosis^{7,8}. It is for this reason that its use is considered appropriate fundamentally in patients at high risk of fracture and for those in whom there has been earlier failed treatment⁹.

Physiological basis

The fundamental physiological action of parathormone (PTH) is the maintenance of the homeostasis of calcium, maintaining practically constant its concentration through the tubular reabsorption of calcium, and stimulating the absorption of calcium in the intestine by means of vitamin D, since it increases renal 1- α hydroxylase.

The effect which PTH exerts on the skeleton is complex. For example, a high and sustained level of PTH, observed in primary and secondary hyperparathyroidism, provokes an increase in bone resorption by its action on osteoclasts, producing secondary osteoporosis. On the other hand, high levels in intermittent peaks increases osteoblastic bone formation activity. This is the effect induced by administering PTH as a treatment for osteoporosis. In both schemes of stimulation of the receptor by the hormone, different genes are regulated which drive the stimulus for the resorption in the case of continuous exposure and formation with intermittent exposure.

The osteoblasts are the cells responsible for bone formation and principal protagonists of bone remodelling which the receptor of PTH expresses.

By means of growth factors modulated by PTH, the stimulation of the proliferation and the later maturation of the osteoblastic progenitors are produced¹⁰. Likewise, PTH induces the transformation of bone covering cells and of the osteocytes in active osteoclasts¹¹, and also increases the average life of the osteoblasts by a reduction in apoptosis¹². The synthesis of PTH takes place in the parathyroid glands. Calcium is the most important signal in the regulation of the secretion of PTH. In the parathyroid glands, an increase in ionized calcium inhibits the secretion of PTH by increasing the intracellular calcium¹³, whilst when it decreases an immediate response is produced with an increase in the secretion of the hormone and a reduction in its degradation and, subsequently, a late response with an increase in genetic expression and in the proliferation of parathyroid cells. This mechanism contrasts with that which happens in the majority of cells, where the secretion is stimulated by an increase in calcium.

The cells of the parathyroid gland have a receptor in their surface which acts as a sensor for levels of blood calcium¹⁴ and also regulates the response of the C cells of the thyroid gland for the secretion of calcitonin. By means of a chain of intracellular signals the secretion of parathormone (PTH) will be produced.

Once released, PTH will increase the resorption of calcium, principally in the distal convoluted tube, and will inhibit the resorption of phosphate in the renal proximal tube, causing hypercalcemia and hypophosphatemia. Also produced is an inhibition of the Na⁺/H⁺ pump and the resorption of bicarbonate, causing mild hyperchloremic metabolic acidosis.

PTH receptor

PTH carries out its biological function by means of a receptor which is a membrane glucoprotein with a molecular weight of 80,000 Da. It belongs to the superfamily of transmembrane receptors linked to G proteins. It is formed of a circle of helices which surround a polarised centre and from which two chains split, one extracellular, aminoterminal, and one domain intracytoplasmatic carboxyterminal. The receptor for classic PTH recognises the extreme amino-terminal of the hormone and also of the protein related to parathormone (PTHrP) with a similar affinity in both cases, for which reason it has been called the PTH/PTHrP receptor¹⁵.

The interaction of PTH or PTHrP with its receptor produces the activation of proteins Gs and Gq. In its turn, the activation of the G protein activates the production of adenylyl cyclase and of the protein Gq activates phospholipase C. The adenylyl cyclase pathway plays an important role in the induction of biological effects, while phospholipase would play a modulating role. Similarly, the activated receptor also induces the expression of the genes and induces growth factors like IGF-I, IGF-II, and TGF- β .

The action of PTH in resorption and mobilising calcium is mediated essentially by the RANK/RANKL system in response to a sustained

exposure to the hormone. Experimentally, an increase in RANKL and an inhibition in osteoprotegerin (OPG) is observed, increasing its quotient. The addition of OPG to the medium blocks the hypercalcemic action of the hormone.

Here also, the intermittent administration of the hormone inverts the equation, since it induces an elevation of OPG with an inhibition of RANKL, again in favour of an anabolic effect. In addition the action of PTH on the osteocytes is transcended by this anabolic effect since it diminishes the expression of sclerostin (SOST). Given that this protein blocks the activation of the Wnt/LRP5-6 pathway, it has an inhibitory effect on osteoblast activation. Therefore, when PTH inhibits it, it "frees" the Wnt/LRP5-6 signalling pathway with the consequent stimulation of bone formation.

Preclinical basis for using PTH

The use of PTH was initiated in the first quarter of the 20th century. In 1925 an extract of parathyroid was purified which showed great anabolic bone activity. However, it has been in the last 30 years when its clinical use has been postulated definitely, following various studies using animal models (rats, rabbits and primates) highlighted its powerful anabolic action, although this had already been detected by Albright in the 40s.

It is in the 1970s when the fragment 1-34, or teriparatide, is synthesised. The first studies carried out in rats confirmed this action on bone. However, what was notable was the different response produced according to the method of administration – continuous or pulsed¹⁶. In both cases an increase in the formation of bone was produced, but a continuous administration also resulted in an increase in resorption and as a result, bone loss, as in the case of hyperparathyroidism. While an intermittent administration did not modify resorption, privileging the forming effect¹⁶. The mechanism by which this different response is produced is not well known. It is suggested, though, that when the administration of the hormone is intermittent the activation of the RANK/RANKL system produced is transitory and negligible. Thus it inhibits osteoblast apoptosis and stimulates its recruitment, which increases the bone-formative action. In animal models it has been shown that intermittent PTH would stimulate the differentiation and activity of the osteoblasts.

Animal models. Rat models

One of the first animal models, employed in the study of the effects of PTH on bone formation was the rat. The use of different types of rat (overiectomised, orchietomised, or studies with young rats) allowed the discovery of what produced an increase in vertebral trabecular bone in which bone mass increased¹⁷. Studies were also carried out to analyse the change in the biomechanical properties of bone observed after treatment with PTH (1-34), an increase, dependent on dose, in the both the formation of cortical bone, and the circumference and resistance of the femur¹⁸. In these rat models it has been found that PTH induces an increase in both number

and activity of the osteoblasts, measured by the synthesis of collagen and osteocalcin in ovariectomised rats. PTH acts principally on trabecular bone, however, it has been observed that the action is different according to different bones. Thus, after 6 months of treatment, connectivity between trabeculae was re-established to a marginal extent in areas such as the proximal tibia, while in the vertebral trabecular bone the recuperation was much greater¹⁹. The reparative effect of teriparatide is dependent on the dose, such that in the case of ovariectomised rats administration of 8 µg/kg would produce a recuperation of bone mass to the level prior to the oophorectomy, whilst a dose of 40 µg/kg increased it above the baseline level²⁰.

Animal model with rabbits

For the study of the behaviour of cortical bone after treatment with PTH the animal model with rabbits was resorted to, since they have a structure and remodelling most similar to humans.

It was observed how, after prolonged treatment with teriparatide at high doses (40 µg/kg), an increase in bone turnover was produced, as well as an increase in cortical porosity which could theoretically worsen the biometric parameters. However, these changes compensate for an increase in the formation of periostic and endostic bone, which brings with it an increase in bone resistance. However, at the start of treatment due to this increase in porosity and turnover an increase in fractures could arise. Paradoxically, in studies designed to assess this extreme no such changes were found. The distribution of cortical porosity was studied, observing that this was higher in the two internal thirds. On the other hand, in the external third this increase in porosity was not found, which is also given as a result an increase in resistance²¹. Subsequently these results have been confirmed in human cortical structure.

Animal model in primates

The last step in the study of the effect of antiosteoporotic drugs on the bone is the animal model with primates, with bone most similar to humans and a skeletal arrangement and share of cortical-trabecular bone also similar.

In these animals it is observed how teriparatide increases BMD in the axial and peripheral skeleton. In ovariectomised animals a dose of 5 µg/kg/d obtained an increase in trabecular bone without a significant change in phosphocalcium metabolism. This effect was maintained for 6 months after the withdrawal of treatment.

Clinical use of PTH

The first indication for teriparatide has been for the treatment of established osteoporosis in postmenopausal women. Of the different studies of this drug which exist, in those which analyse the reduction of fractures, one that stands out is a study called FPT (Fracture Prevention Trial), published by Neer et al.⁶, which was the reference study for the drug, in which teriparatide at doses of 20 or 40 µg/day

were compared against a placebo in 1,637 postmenopausal women with vertebral fractures. In addition, all participants received calcium and vitamin D supplements. At approximately two years of treatment it was found that both doses of teriparatide achieved significant reductions in the rate of new vertebral (65% and 69% reduction respectively) and non-vertebral (53% and 54% respectively) fractures. The effect on the reduction in risk of multiple vertebral fractures was 77% and 86% respectively, and of moderate or severe vertebral fractures, 90% and 78% respectively. In increase in lumbar bone density was also produced (9.7% and 13.7%) and in the femoral neck (2.8% and 5.1%). Although with 40 µg/day greater effects on BMD were achieved the risk of fracture was not significantly different between the two doses, whilst the higher dose was less well tolerated (11% abandonment due to undesirable effects with 40 µg/day, as against 6% with 20 µg/day or placebo) for which reason 20 µg/day was selected for clinical use. This study was initially planned to have a duration of 36 months, but was suspended when the patients reached 21 months as a safety measure because in the study of the drug's toxicity in Fisher rats found cases of osteosarcoma. Subsequently in complementary studies there was evidence that this was only produced in young rats, with bone in full development and which had high doses of the drug^{22,23}. Despite this precautionary suspension, subsequent exhaustive studies in animal models, as well as a detailed follow up of treated patients showed a reliably positive safety profile which allowed the drug's continued development and clinical use.

A subgroup of patients were followed over the long term, up to 18 months after the cessation of treatment. The subgroup of women who had received teriparatide continued to have a 40% reduction in the risk of vertebral fracture at 18 months in comparison with the placebo group. These results suggest that the benefit regarding the incidence of non-vertebral fractures after a year and a half of treatment with teriparatide would persist for three years after the treatment having ended^{24,25}.

Another trial has compared teriparatide (40 µg/dia) with alendronate²⁶ in a group of 146 postmenopausal women. After 14 months of treatment the BMD in the lumbar spinal column had increased significantly, more with teriparatide at 40 µg/day than with alendronate (15.1% vs 6.6%); the same happened for the BMD in the femoral neck. However, this study had a reduced sample size and an insufficient period of follow up, which meant that the number of fractures accumulated was also insufficient, for which reason it was not possible to draw conclusions from them as to the drug's antifracture efficacy.

Combined treatment

Nowadays the bisphosphonates are the foundation for treatment of osteoporosis. There have been a number of trials to see if their association with teriparatide has a beneficial effect.

In a randomised trial carried out with 83 men affected by osteoporosis, the effects on bone of alendronate at a dose of 10 mg/day, of teriparatide at 40 µg/day, and a combination of both, were compared²⁷. At the end, after 30 months of alendronate and 24 months of teriparatide a statistically significant increase in BMD in the lumbar spine was observed in the group who received only teriparatide as against those who received the combination. In addition, it was notable that the BMD in the femoral neck was higher at 30 months in the group which received only teriparatide. This might suggest that if both drugs are administered simultaneously, not only does it not strengthen them but it appears to inhibit them, and that their association would reduce the anabolic effect of the teriparatide in trabecular bone in the spine and would alter the capacity of the teriparatide to increase the cortical volume of the femur during the first months of treatment.

Recently, at the ASBMR congress the preliminary results of a study were presented in which it was observed that the combined administration of zoledronic acid and teriparatide resulted in a greater increase in BMD of the total femur than teriparatide alone²⁸, which suggests that when the cells have not yet received the inhibitory effect of the induced remodelling by the antiresorptives the response the teriparatide. is maintained.

Teriparatide in previously treated patients

Seeing as these antagonistic effects which the combination of the two drugs appears exert one might ask if at the start of treatment with teriparatide when there has been previous treatment with anti-resorptives, especially biphosphonates, the anabolic effect of teriparatide is influenced. For this reason, a study, the EUROFORS study, was carried out which evaluated the response in BMD and safety issues, in a group of 503 postmenopausal women with osteoporosis who received teriparatide for 24 months. They were classified into three groups: those who had not received previous treatment; those who, having been receiving treatment, did not show any evidence of its failure; and finally, those who had had an inadequate response to this treatment. Although bone mass increased significantly in all three groups, and in the group not having received previous treatment with teriparatide produced a higher increase in bone mass in the lumbar spine, there were also significant increases in the other groups²⁹, without statistically significant differences between them. These results guarantee that even in patients on prolonged treatment with antiresorptives, we could expect a powerful formative effect when changing over to teriparatide.

Sequential therapy

We have seen how the use of teriparatide after an antiresorptive treatment retains its full effect, whilst its concomitant use brings a somewhat limited benefit, in some studies, in relation to the use of teriparatide alone. However, starting antiresorptive treatment, after having carried out bone

forming treatment with PTH 1-34, to consolidate the formed bone could have advantages. It is not clear what treatment should be started after having completed treatment with teriparatide in serious osteoporosis. There are clinical trials which show how the administration of an antiresorptives after having ended treatment with teriparatide has a protective effect on the gains in bone mass achieved. The most recent of all, an extension of the trial already cited, EUROFORS³⁰, a prospective, randomised and controlled trial, compared bone mass and clinical safety with three options for treatment after a year with teriparatide. These three options are: continue for a second year with teriparatide; start treatment with raloxifen; or do not carry out treatment. It was observed that in the group which continued to receive teriparatide bone mass in the hip increased by 2.5%, while the same increase was 2.3% in the case of raloxifen, and 0.5% in those patients who received neither drug, although the study was not strong enough to assess their effect on fractures. These results allow us to conclude that continuing therapy after completing treatment with teriparatide has a beneficial effect, since it consolidated the increase in bone mass achieved thanks to the bone forming treatment. Teriparatide, an anabolic agent, induces a period of formation or "recovery" which is then followed by the effect, by the antiresorptive, of "consolidation" of the gains in bone mass.

Osteoporosis induced by corticoids

There are, similarly, trials which show the efficacy of teriparatide in the treatment of osteoporosis induced by systemic corticoids^{31,32}. In a randomised, double blind study 428 patients²⁸, of both sexes, with ages between 22 and 89 years, who had received corticosteroids for a period of at least 3 months, were allocated to two groups, one which received 10 mg/day of alendronate while the second was treated with 20 µg/day of teriparatide, both for a period of 36 months. Set as a primary objective was the change in BMD in the lumbar spine at 18 months, and as secondary objectives, markers for bone resorption, total BMD in the femur, and the incidence of fractures and safety. Statistically significant differences were attained with respect to BMD in the lumbar spine in favour of teriparatide at 6 months. At 12 months, the total BMD in the femur was higher in the teriparatide group, and at the end of the study, as well as the higher gains in bone mass, fewer vertebral fractures had been produced in the teriparatide group with respect to the alendronate group, the difference being statistically significant. Steroid osteoporosis, and male osteoporosis, will be commented on in more detail in other chapters of this monograph.

Treatment of male osteoporosis

Teriparatide has also been used in men with osteoporosis³³. A group of 433 men with densitometric osteoporosis, of idiopathic origin, or due to hypogonadism, randomly received either placebo or teriparatide at 20 or 40 µg/day. They also received

calcium and vitamin D. After an average of 11 months of treatment the BMD in the spinal column increased by 5.9% and 9.0% for the doses of 20 and 40 µg/day respectively, both significantly different from the placebo group ($p < 0.001$). In the femoral neck the increases were 1.5 and 2.9% for the two doses, again, both significantly different from the placebo. The increases were independent of the state of the gonads and other factors, and of a similar magnitude to those observed in the FPT reference study in women.

Teriparatide and adverse effects

The most frequent secondary effects described in the clinical trials have been nausea, pain in the extremities, headache and dizziness. There have been cases described of orthostatic hypertension, above all after the first dose, which do not require the interruption of treatment.

Treatment with teriparatide provokes a discrete raising of blood calcium which reaches a maximum at 4-6 hours after the subcutaneous administration of the drug, and which normalises itself after 16-24 hours. While it is not recommended to carry out a follow up of the calcemia, the presence of baseline hypercalcemia is considered to be a contraindication. As we have said earlier, in studies with Fisher rats, teriparatide has been associated with an increase in the incidence of osteosarcomas. This finding provoked an interruption of three clinical trials in humans which were under way, and the carrying out of experimental safety studies. The conclusions which were drawn from the results are that the dose and the duration of treatment are the main factors related to the appearance of sarcomas of this type specific to rats. However, there are notable differences between bone tissue of rats and that of humans. In addition, the study dealt with young rats in the full development phase, and the dose of teriparatide was extraordinarily high and administered during practically the whole life of the animal. All these factors put in doubt the validity of this Fisher rat model, since, in addition, the results of numerous studies in other animal models have been totally negative. In the studies carried out in primates with the administration of such high dose as 5 µg/kg over 18 months, not a single bone tumour has been seen. In the case of humans, not a single case of osteosarcoma has been observed after treatment with teriparatide over 18 months or in the three year follow up after the end of treatment. The exhaustive re-evaluation of the follow up data on all the patients treated, on the part of the evaluation agencies of North America and Europe, has concluded that the use of teriparatide is safe in human beings, there not having been observed a higher incidence of bone tumours than in the general population.

However, and as an additional precaution, teriparatide is formally contraindicated in those patients who present a high risk of osteosarcomas (Paget's disease, or inexplicably high levels of alkaline phosphatase), patients at an age of bone growth, those with systematically treated neoplasia, and those who have had skeletal X-rays.

Conclusions

Fractures are principal consequence of osteoporosis, both for their cost in terms of health and for their reduction in the quality of life of patients. The development of drugs which allow an ever greater reduction in the risk of fractures permits not only an increase in the therapeutic arsenal but one which diminishes the incidence of the most serious consequence of such a prevalent disease. For this reason, the appearance of this new group of treatments called bone formers or anabolics is important, since, specifically, teriparatide reduces vertebral and non-vertebral fractures, which on the one hand makes available a new anti-fractural option which acts specifically on the process of bone formation, and on the other, it reverses bone deterioration due to osteoporosis. This is so because teriparatide does not only produce a significant increase in BMD as a consequence of the net formation of bone, but it also improves the microarchitecture and the biomechanical properties of this bone. Comparative studies with other drugs have been favourable to teriparatide, both in terms of bone mass and in the reduction of risk of fractures. For all these reasons, teriparatide is a first line option in the treatment of patients with serious osteoporosis, such as those listed in the guide to clinical practice of the Spanish Society for Bone and Mineral Metabolism Research (SEIOMM)³⁴ (http://www.seiommm.org/documentos/osteoporosis_es_en.pdf). This all means that we have available more therapeutic options in our fight against the most prevalent bone disease, osteoporosis.

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