Odanacatib: a possible new therapeutic option for the treatment of osteoporosis

Cathepsin K is a protease released by osteoclasts, which is involved in the destruction of collagen fibers that form the organic phase of the bone matrix, and plays a key role in bone resorption. Odanacatib is a selective inhibitor of cathepsin K, which blocks bone remodeling by inhibiting resorption. Phase II trials have shown that odanacatib is a potent antiresorptive agent and does not significantly reduce biochemical markers of bone formation during long-term treatment of postmenopausal women. This increases the bone mineral density that is comparable with the most powerful antiresorptive agents. Odanacatib has a generally favorable tolerability and safety profile. Currently, only Phase II studies have been reported and its efficacy in reducing fractures has not been demonstrated. The adverse effects are reversible and disappear after discontinuation. If this antifracture efficacy can be shown, odanacatib could be a safe, efficacious option for the treatment of osteoporosis.

KEYWORDS: cathepsin K ■ odanacatib ■ osteoclast ■ osteoporosis

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Throughout life, bone remodeling maintains the structure of bone tissue, leading to changes in bone density, shape and strength that allow it to adapt to biomechanical circumstances at any given time. This remodeling occurs both in cortical bone, which is responsible for load bearing, and in trabecular bone, which participates in the regulation of mineral homeostasis and bone strength. Bone remodeling consists of an initial phase of bone resorption followed by a phase of formation, both of which are regulated by general (endocrine) and local (paracrine) factors [1].

Osteoclasts are the key element in bone resorption. Osteoclasts are derived from the mononuclear phagocyte system, and their proliferation and maturation is stimulated by a protein, RANKL, whose blockade is a therapeutic target in osteoporosis. Once mature, osteoclasts bond to the bone surface via actin-rich podosomes, forming cavities known as resorption lacunae. The secretion of protons by the cell creates an acid medium within the lacunae, which destroys the mineral phase of bone; the calcium hydroxyapatite crystals. Subsequently, the osteoclasts secrete cathepsin K, which dissolves the organic component of the bone matrix (consisting mainly of collagen) [2]. Cathepsin K was first identified by Tezuka *et al.* using a differentiation screening method [3]. The relationship between cathepsin K and bone mineral density (BMD) is confirmed by findings in a rare human osteopetrotic disease, pycnodysostosis, in which loss of function is secondary to mutations in the gene that codes for cathepsin K, causing an increase in BMD, low stature, cranial deformities and acroosteolysis of the distal phalanges [4]. In addition to osteoclasts, osteocytes secrete cathepsin K, although their function remains unknown.

Cathepsin K is a lysosomal protease that belongs to the papain-like cysteine protease family, which is coded by a gene located on chromosome 1q21. Its structure is formed of an amino-terminal region of 15 amino acids, a propeptide of 99 amino acids and a catalytic unit of 215 amino acids. The gene can be stimulated by various factors, mainly bone-resorption stimulating cytokines [5,6].

At present, there are no available data on the antifracture efficacy of odanacatib. Therefore, the objective of this article is limited to summarizing the results of preclinical and clinical studies on the effectiveness of odanacatib.

Osteoporosis is a disease of bone remodeling, with resorption predominating over formation, causing an imbalance. Thus, it seems reasonable to use drugs that inhibit bone resorption to correct this imbalance. Among the possible therapeutic targets, cathepsin K inhibition is attractive, since it inhibits destruction of the organic component of the bone matrix without affecting osteoclasts, either quantitatively or qualitatively. This has led to the development of drugs that inhibit cathepsin K and to the evaluation of their efficacy and safety in the treatment of osteoporosis.

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Odanacatib clinical development

The efficacy and safety of various cathepsin K inhibitors, a new class of antiresorptive drugs, have been studied. Some potential agents were retired during Phase II clinical studies owing to the appearance of severe dermatological side effects. Odanacatib is a powerful, selective inhibitor of cathepsin K that blocks the proteolytic activity of the enzyme. Its chemical structure contains a phenyl ring that substitutes the P2–P3 amide bond of a amino acetronile dipeptide 1. Its potency and selectivity are due to the presence of the 4-fluoroleucine side chain at the P2 position interacting within the S2 pocket [7]. As it is selective, dermatological side effects have not been observed as it does not inhibit other types of cathepsin located in the skin [8] that cause adverse cutaneous effects [9].

Drug development consists of two main phases: preclinical trials in animals and clinical trials in patients and healthy volunteers.

Preclinical phase

Several experimental studies have examined the possible role of cathepsin K in bone remodeling and, therefore, as a therapeutic target. The first studies were carried out in cathepsin gene knockout mice and found that osteoperosis was associated with a reduction in bone resorption. Pennypacker *et al.* found an increase in cortical and trabecular bone volume, with an increase in the number and thickness of trabeculae in the distal femur in a group of homozygote cathepsin K-null mice [10]. Moreover, transgenic mice overexpressing cathepsin K had a lower BMD associated with increased bone remodeling [11]. However, this model is not adequate to assess the efficacy of cathepsin K inhibitors intended to be used in humans, due to the low homology in the active form of the enzyme between humans and rodents. Models using rabbits and, especially, monkeys, are preferable.

In an ovariectomized rabbit model, odanacatib administered for 27 weeks was compared with placebo and alendronate. Odanacatib prevented estrogen deficiency-related bone loss at the lumbar spine as alendronate. The non-ovariectomized rabbits showed the same bone mineral density. BMD increased in a dose-dependent manner in the total hip and femoral neck. Interestingly, bone formation was maintained in all sites analyzed and the biomechanical properties of bone were preserved [12].

Two studies have been conduced to evaluate the effect of odanacatib on BMD, markers of bone remodeling, biomechanical properties and histomorphometric studies at the lumbar spine and hip in ovariectomized monkeys. In one study, 42 female rhesus monkeys (*Macaca mulatta*) aged 13–23 years were administered two doses of odanacatib at exposures below or similar to those subsequently used in the human Phase III trial [13,14]. An increase in BMD and bone turnover was observed in the lumbar spine for both dosages used. There were differences in the biomechanical properties of bone between control monkeys and treated ovariectomized monkeys. Interestingly, odanacatib affected TRAP-5b, a marker of resorption, which also reflects the number of osteoclasts. This marker remained stable during the length of the trial, indicating that there was no reduction in the number of osteoclasts.

An increase in BMD was observed at the hip, with increased cortical thickness reflecting the reduction of bone resorption at this level. This was accompanied by increased bone formation in the periosteum, which increased the diameter of the femoral neck and resistance to fractures.

Thus, experimental studies show that odanacatib can increase BMD at the hip and lumbar spine, blocking bone resorption in ovariectomized animals while maintaining the biomechanical properties of bone. Notably, the number of osteoclasts remained stable and, in the hip, there was increased periosteal bone formation and preserved endocortical formation, leading to an increase in femoral neck bone strength, resulting in a reduction in fractures.

Phase I study

Phase I studies are aimed at determining the pharmacokinetic and pharmacodynamic properties of the drug, testing for safety and tolerability, and calculating dosages and dosing schedules. They are typically conducted in healthy volunteers and usually include a sample size of 30–60 individuals in a given study. In the case of odanacatib, the literature reports a study performed to evaluate the efficacy and safety of daily and weekly doses of odanacatib administered to characterize the pharmacokinetics and pharmacodynamics of the drug. The study population included 79 postmenopausal women, whose hormonal situation was defined as the absence of menstruation during the previous 3 years or the previous year with confirmation of an elevated follicle stimulating hormone level in the postmenopausal range. The study was randomized, placebo-controlled and double-blind. Efficacy was assessed by measuring changes in markers of bone formation and

resorption. The following markers were measured: CTx, 1-CTP, TRAP5b, uDPD, BSAP, osteocalcin and NTx/Cr. CTx and NTx are generated by the catalytic action of cathepsin on collagen, but DPD is not influenced by the effect of odanacatib on the processing of collagen. Four weekly doses (5, 25, 50 and 100 mg) and three daily doses (0.5, 2.5 and 10 mg) were compared with placebo. A reduction in markers of resorption was observed while little effect was seen on markers of bone formation. The lack of reduction in the formation markers was not surprising given the relative short duration (3 weeks) of the study. The temporal antiresorptive behavior was similar to the daily and weekly doses, with the nadir being observed within several days of administration of the drug, with no meaningful differences being found between the schedules tested. The suppression of markers was dose dependent, although not dose proportional. The effect was greatest for the highest weekly doses (50 and 100 mg) and the daily doses of 2.5 and 10 mg. The pharmacokinetics showed that the half-life of the drug was between 66 and 93 h. These results show that weekly administration of odanacatib is possible. No meaningful differences between odanacatib and placebo were observed in the number of adverse effects [15]. These results were supportive of selecting, the weekly dosing regimen of odanacatib for use in the Phase II trial.

Phase II trial

Phase II clinical studies are performed in patients with osteoporosis and are intended to assess the efficacy of the drug at different doses, by measuring changes in bone remodeling markers and BMD. A second aspect is to assess safety compared with placebo.

The 5-year follow-up data are currently available. Initially, a randomized, double-blind, placebo-controlled, multicenter study was carried out, which enrolled 399 postmenopausal women. Menopause was defined as no menstruation during the previous 5 years or bilateral oophorectomy. Women aged between 45 and 85 years were included. The densitometric criteria for inclusion were a T-score less than -2 but not less than -3.5 at any site.

Therapeutically, patients were divided into five groups according to the dose: placebo, 3, 10, 25 and 50 mg/week. All patients received supplements of vitamin D3 (5600 IU weekly) and calcium (500 mg/day of calcium carbonate). The primary objective was to measure changes in bone mass at the lumbar spine and the secondary objectives were to measure changes in BMD in other sites, changes in marker of bone remodeling and resorption, and the safety of the drug.

The duration of the study was 24 months. Of 399 women randomized, 331 (83%) completed 12 months of treatment and 270 patients (70%) completed 24 months. No differences were found between women who completed or abandoned the study. In the third year, women in each of the original treatment groups were re-randomized to odanacatib 50-mg weekly or placebo. In this period, 189 women participated, of which 169 (87%) completed the study. In the fourth and fifth years, women who received placebo or 3 mg of odanacatib in the first 2 years or placebo in the third year were switched to weekly odanacatib. Therefore, in the last 2 years, 100 women received odanacatib and 41 placebo. Results have been published for the first 3 years [16,17], while the results from the fourth and fifth years have been reported in congress abstracts [18,19]. The available data are divided into the following sections: bone turnover markers, BMD, adverse effects and reversibility.

Markers of bone remodeling

Resorption markers (uNTx/Cr, sCTX and uDPD) were significantly reduced in a dose-dependent fashion during the first 6 months. Subsequently, these values tended to increase, reducing the differences with placebo, especially at doses <50 mg weekly. Only the highest doses showed statistically significant differences with placebo at 24 months, with uNTx/Cr falling by 60%, sCTX by 40% and uDPD by 30%. At 36 months, the reductions were 50% for uNTx/Cr, 24% for sCTX and 17% for uDPD/Cr. Complete results are not available for all markers in the extension studies at 48 and 60 months, whose results have only been presented in congress abstracts, but there was a reduction in sCTX of 41% at 48 months and a reduction in uNTx/Cr of 67% at 60 months (TABLE 1).

Markers of bone formation behaved differently. Bone alkaline phosphatase and PINP were evaluated and the reduction in these markers was 20% for both at 24 months, much less marked than those of resorption markers.

At 36 months, there was an increase in bone alkaline phosphatase (18%) and a very small reduction in PINP (6%). At 48 and 60 months, there was a small reduction in bone-specific alkaline phosphatase (2 and 16%, respectively). The behavior of odanacatib at the level of bone

Table 1. Effect of 50 mg of odanacatib on markers of bone formation and resorption at 12, 24, 36, 48 and 60 months.

	12 months	24 months	36 months	48 months	60 months
BSAP (%)	-18.0	-15.0	+18.0	-2.0	-16.0
NTx/Cr (%)	-60.2	-51.8	-50.0	–	-67.4
CTx (%)	-60.0	- 45.0	-24.0	-41.0	–

BSAP: Bone-specific alkaline phosphatase; CTx: Carboxyterminal telopeptide of type I collagen; NTx/Cr: N-terminal telopeptide of type I collagen normalized to creatinine.

remodeling is different from that of bisphosphonates and PTH. There is a dissociation between markers of bone resorption and formation that could improve the quantity and, especially, the quality of bone formed.

In the study at 36 months, assessment of two resorption markers, TRACP 5b and 1CTP, showed both were increased. TRAC 5b is of particular interest since it is an indicator of the number of osteoclasts. These results, confirmed by histomorphometric studies, show that the number of osteoclasts is not reduced but is normal or increased. This is likely to allow communication with the osteoblasts that explains the behavior of the formation markers. *In vitro* studies have shown that cathepsin K inhibitors increase supernatant levels of osteocalcin, IGF-1 and BMP2 [20]. Under normal conditions, these factors are degraded in the hemivacuole formed in the basal surface of osteoclasts. By blocking cathepsin K this destruction can be avoided, allowing these factors to stimulate the osteoblasts [21].

Bone mineral density

The results showed a dose-dependent increase in BMD in all sites throughout the entire study. The only slight reduction was observed in the distal third of the radius. Table 2 shows the results for the 50-mg weekly dose used in the Phase III study.

Safety

The safety of odanacatib was evaluated by collecting adverse events during the 5 years of the Phase II trial. These results will be completed using the data from the Phase III trial. Previous studies of cathepsin inhibitors were discontinued owing to severe cutaneous adverse events. Therefore, the results at 2 years specifically evaluated cutaneous, together with respiratory, adverse events. No dose-dependent effect was observed with respect to cutaneous adverse events, and there was no higher incidence of respiratory adverse events (nine patients in the placebo and six in the odanacatib groups). Only one severe cutaneous adverse effect was observed (squamous cell carcinoma in a patient receiving a dose of 25 mg). During the first 3 years, no differences were observed between placebo and 50-mg odanacatib (Table 3). The most common side effects were back pain, arthralgia, pain in an extremity and nasopharyngitis, with similar incidence between patients treated with odanacatib and placebo. The incidence of skin side effects was 16% in the placebo group and 12% in the odanacatib group, with no cases of morphea recorded. Nonsevere laboratory abnormalities occurred in ten patients in the placebo group and eight in the odanacatib group, but no changes in calcium levels were found. There was a higher incidence of urinary tract infections at 3 years (3% placebo vs 12% odanacatib), results were not confirmed at 48 and 60 months. Urinary tract infections were diagnosed by primary care physicians and urine cultures were available in only one case [16,17]. There is no data on osteonecrosis of the jaw or atypical femoral fracture. The lower antiresorptive potential of odanacatib may avoid these adverse effects.

Bone safety was assessed in 32 patients at 24 months, but four biopsies could not be evaluated because of the poor quality of the samples. No abnormalities or differences with reference

Table 2. Effect of 50 mg of odanacatib on bone mineral density.

	24 months	36 months	48 months	60 months
Vertebral BMD (%)	+5.7	+7.9	+10.7	+11.9
Hip BMD (%)	+4.1	+5.8	+8.3	+8.5
Femoral neck BMD (%)	+4.7	+5	+8.9	+9.1
Distal radius BMD (%)	+2.9	-0.4	-0.12	-1

BMD: Bone mineral density.

Table 3. Adverse events at 24 and 36 months.

	24 months		36 months	
	Placebo (n = 83)	*Odanacatib, 50 mg (n = 78)*	*Placebo (n = 92)*	*Odanacatib, 50 mg (n = 97)*
Adverse events (%)	77 (92.8)	72 (92.3)	74 (80)	76 (78)
Serious adverse events (%)	8 (9.6)	14 (17.9)	8 (9)	10 (10)
Cutaneous adverse events (%)	19 (22.9)	19 (24.4)	15 (16)	12 (12)
Respiratory adverse events (%)	9 (10.8)	10 (12.8)	7 (8)	7 (7)
Discontinuation owing to adverse events (%)	11 (13.3)	13 (16.7)	4 (4)	4 (4)
Discontinuation owing to serious adverse events (%)	0 (0)	3 (3.8)	0 (0)	1 (1)
Discontinuation owing to cutaneous adverse events (%)	2 (2.4)	4 (5.1)	0 (0)	0 (0)

values were found. Transiliac biopsy results showed a decrease in the frequency of activation, mineral apposition rate, and bone formation rate (surface referent and bone volume referent) with the 50-mg doses. The mineralization lag time was increased. No giant osteoclasts were observed [16].

Reversibility

To determine whether the effect of odanacatib was maintained over time or disappeared after withdrawal, patients in each of the odanacatib treatment groups were switched to odanacatib 50-mg or placebo in a 1:1 ratio at 24 months. In patients switched to placebo, initially, there was a sharp increase in markers of bone resorption and formation, with a progressive decrease at 36 months, and with no differences with placebo being found except that uNTx/Cr remained high (25% at 36 months). BMD decreased sharply at all sites, mostly during the first 6 months, although it remained above initial values [16]. These results should be taken into account when administration of odanacatib is suspended. Treatment duration and the possibility of continuing with other therapies that modulate the increase in bone remodeling should be considered.

Phase II studies show that odanacatib at a dose of 50 mg has an antiresorptive effect, with little inhibition of bone formation and a progressive increase in BMD, which is maintained during the 5 years of treatment. The results, in terms of BMD, are comparable with denosumab, the most potent antiresorptive agent, although the number of patients studied is fewer at present. Odanacatib has a favorable safety and tolerability profile and its effects are reversible.

To demonstrate efficacy and receive regulatory approval, an osteoporosis treatment must demonstrate its ability to reduce fractures, especially hip fractures, which cause the greatest morbidity and mortality. For this reason, a Phase III clinical trial has been designed, which includes over 16,000 postmenopausal women [101]. The target population is postmenopausal osteoporotic women aged ≥65 years with a T-score at the femoral neck or total hip of ≤-2.5 or with a prior vertebral fracture and a T-score at the femoral neck or total hip of ≤-1.5.

The exclusion criteria are similar to those of other pivotal studies. This is a clinical, randomized, double-blind, placebo-controlled trial. All patients will receive vitamin D supplements (5600 U weekly). Women with insufficient calcium ingestion will also receive supplements. The primary objective of the study is to reduce hip, vertebral and nonvertebral fractures. The length of the study is not fixed. The study will end when 237 hip fractures have accrued. A number of vertebral, nonvertebral and hip fractures that allow statistically significant differences to be established will be necessary.

Odanacatib & bone metastases

Cathepsin K is an enzyme that, in addition to its role in resorption, may contribute to the growth and progression of tumors, especially bone metastases. This is determined by the release of growth factors from the extracellular bone matrix, and the upregulation of odanacatib, with an increase in its expression, in breast cancers [22,23]. One Phase II study with a small number of patients (n = 43) with breast cancer and bone metastases has compared the antiresorptive effect of odanacatib versus zoledronate. The follow-up period was 1 month and the doses were 5 mg/day of oral odanacatib and 4-mg monthly of intravenous zoledronate. Both drugs produced similar reductions in resorption from baseline (77% reduction in NTx vs 73%, respectively). These results suggest that odanacatib may be a new therapeutic

option in the treatment of patients with tumors and metastatic bone disease [24].

Conclusion

Odanacatib is a cathepsin K inhibitor whose mechanism of action differs from that of other antiresorptive agents. The reduction of resorption is lower than that of other powerful antiresorptive agents. However, the increase in BMD is similar or greater. The decoupling between resorption and formation, with a greater reduction in resorption than in formation, may explain this effect. Odanacatib does not reduce the number of osteoclasts and/or alter their function. The effects of odanacatib are reversible and the drug has a generally favorable safety and tolerability profile. The results of the ongoing Phase III trial are required to confirm the possible effect of odanacatib in reducing fractures.

Future perspective

Bisphosphonates with calcium and vitamin D (alendronate, risedronate and zoledronate), the current gold standard in the treatment of osteoporosis, are efficacious in reducing osteoporotic fracture [25–27]. However, their use entails various problems and the search is ongoing for alternative or complementary therapies. The efficacy of denosumab, the first monoclonal antibody used in the treatment of osteoporosis, was demonstrated in the FREEDOM study. [28]. The effects of denosumab, unlike those of bisphosphonates, are reversible. Odanacatib, a drug in the same therapeutic group, which has less antiresorptive power but also produces a smaller reduction in bone formation, may prove to be an alternative. Data on the effects of odanacatib on fracture reduction are awaited. One advantage of this class of drugs compared with bisphosphonates is that it is probable that they do not produce severe adverse events such as osteonecrosis of the jaw or atypical fractures that are associated with the latter.

With respect to anabolic drugs, only teriparatide has demonstrated efficacy in reducing vertebral and nonvertebral fractures. Oral, inhaled and transdermal formulations are currently in Phase I studies.

PTHrP is an alternative protein, closely homologous to PTH, which has been speculated to act through various mechanisms. The use of calcilytics, which act on the CaSR receptor to stimulate endogenous secretion of PTH, might be an alternative, although preliminary results are not encouraging. More promising results have been obtained through modulation of the canonical Wnt-signaling pathway, especially by blocking the endogenous inhibitors (sclerostin and DKK1). The most advanced therapeutic option is sclerostin-antibody AMG787/CAP785, which is being tested in a Phase II trial in 400 postmenopausal women [29].

There is increasing interest in drug combinations and sequential therapy. Although drug combinations may be useful in various situations, such as treated fractures, poor adherence

Executive summary

Mechanism of action

- Odanacatib is an antiresorptive agent that acts by selectively inhibiting cathepsin K.
- It maintains the normality and the number of osteoclasts.
- Bone formation is partially preserved.

Pharmacokinetics

- Odanacatib has a long half-life of 66–93 h and, therefore, can be administered weekly.
- Serum levels reach a first peak at 6 h and a second peak at 24 h.
- Serum levels increase proportionally with the dose.

Clinical efficacy

- A dose of odanacatib of 50-mg weekly significantly reduced markers of bone resorption, with less significant effects on markers of formation, and increased bone mineral density in a manner similar to the most powerful comparable antiresorptive agents.
- The effects of odanacatib are reversible and disappear after withdrawal.
- No data are yet available on fractures.

Safety

- Odanacatib is generally safe and well tolerated in clinical trials without severe cutaneous adverse events.
- Phase II studies showed no differences with placebo.

Dosage & administration

- Odanacatib is administered at a dose of 50-mg weekly.

to therapy and severe osteoporosis, no randomized studies have yet assessed their efficacy in fracture reduction, while the number of side effects may be higher. Sequential therapy is currently indicated in some situations such as administration of an antiresorptive drug after teriparatide therapy in order to conserve the benefits obtained [30].

The spectrum of treatments in osteoporosis is gradually widening, and antiresorptive agents and anabolic drugs provide hope for the future. A greater number of treatment options may allow individualized treatment based on the functional situation, the drug intake and the associated comorbidities of each patient [31].

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Website

101 A study of MK0822 in postmenopausal women with osteoporosis to assess fracture risk (MK-0822-018 AM4 EXT). http://clinicaltrials.gov/ct2/show/NCT00529373