Review

New therapeutic targets for osteoporosis: Beyond denosumab

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A B S T R A C T

Treatments for osteoporosis over the last few decades have largely focused on antiresorptive agents that effectively prevent bone loss. Beginning with hormone therapy, a variety of new potent antiresorptive agents were developed, including oral and intravenous bisphosphonates, raloxifene and other selective estrogen receptor modulators, nasal spray calcitonin, and denosumab. Teriparatide and PTH 1–84 are the only approved anabolic agents to date that primarily build new bone density. A variety of new biologic agents that focus on molecular targets important for the stimulation of new bone formation are being developed. Cathepsin K inhibitors appear to have mixed antiresorptive and anabolic actions because they inhibit one of the major osteoclast digestive enzymes without suppressing bone formation, thereby leading to anabolic effects on bone. New biologic agents in clinical trials include anti-sclerostin and anti-dkk1 antibodies that stimulate the Wnt/β-catenin pathway in osteoblasts, leading to new bone formation. These new agents will effectively stimulate new bone formation by different mechanisms, leading to improved bone mineral density and reduced fractures.

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1. Introduction

There is great interest in new therapeutic targets for the treatment of osteoporosis because of variable potency and toxicities of the currently available agents, which have a moderate ability to increase bone density and reduce fractures. Current treatments in many countries include hormone therapy, bisphosphonates, raloxifene, calcitonin, or denosumab. Calcitonin was recently removed from the market in Europe due to concerns regarding cancer with long-term use. Teriparatide (PTH 1–34) and PTH 1–84 remain the only approved agents in some countries that directly stimulate new bone formation. This mini-review will briefly summarize new therapeutic targets for osteoporosis, and briefly discuss the agents being developed against these targets.

2. Antiresorptive agents

Even though most currently approved therapeutic agents primarily prevent bone loss, there is continued interest in development of new antiresorptive agents that offer selective advantages
over existing agents. Because new antiresorptive agents do not markedly suppress bone formation, and may uncouple bone formation from resorption, these compounds may open anabolic windows of variable duration to stimulate new bone formation.

2.1. Cathepsin K inhibitors

The main category of new antiresorptive agents being developed is cathepsin K inhibitors [1,2]. Cathepsin K is a member of the papain family of cysteine proteases. In activated osteoclasts, cathepsin K is a major digestive enzyme that breaks down type I collagen in resorption pits, after hydrogen ions secreted via osteoclast membrane proton pumps have solubilized the hydroxyapatite component of bone. The combined action of cathepsin K, other enzymes, and acid pH within bone resorption pits beneath osteoclasts effectively causes local bone resorption. Because cathepsin K inhibitors selectively target one of the main osteoclast digestive enzymes, but do not inhibit other digestive enzymes, or block acid secretion by actively resorbing osteoclasts, their antiresorptive effect is predicted to be milder than that of more potent antiresorptive agents such as bisphosphonates or denosumab that markedly decrease both bone resorption and bone formation. Cathepsin K inhibitors, like most of the new agents, have rapid offset of action, so patients taken off this type of drug will require addition of another medication to prevent loss of bone previously gained with cathepsin K inhibitor treatment.

Odanacatib (MK-0822) is a new selective cathepsin K inhibitor that causes a moderate sustained decrease in bone resorption, but a lesser and more transient decrease in bone formation, in completed phase I and II clinical trials in postmenopausal women [3–5]. Preclinical studies in mice, rabbits, or monkeys showed that cathepsin K deficiency led to maintenance of, or an increase, in bone formation [6,7]. These changes resulted in a moderate increase in BMD, similar to what is seen with the bisphosphonate alendronate. Odanacatib is undergoing phase III clinical trials in postmenopausal women and older men. Odanacatib may not interfere with osteoclast maintenance or stimulation of new bone formation, unlike bisphosphonates and other available antiresorptive agents, and is believed to uncouple bone resorption from bone formation. This leads to preserved bone formation while bone resorption is moderately decreased, resulting in an anabolic effect for a period of time. No clinically relevant safety concerns were associated with odanacatib.

ONO-5334 is a cathepsin K inhibitor undergoing phase I and II clinical trials [8]. The phase II OCEAN clinical trial [9] showed suppression of bone resorption similar to alendronate, with little or no suppression of bone formation, with different doses of ONO-5334. Lumbar spine, femoral neck, and total hip BMD increased similarly to what was seen with alendronate. No clinically relevant safety concerns were identified with this drug.

Early cathepsin K inhibitors demonstrated undesirable off-target effects such as skin hardening (morpha) that halted their clinical development. Balacatib was reported to cause morpha-like side effects [10], perhaps related to the presence of cathepsin K not just in osteoclasts, but also skin and pulmonary fibroblasts. Similar effects have not been seen with odanacatib, ONO-5334, or other cathepsin K inhibitors still under development.

3. Anabolic agents

Anabolic agents increase bone strength by directly stimulating new bone formation. Many potential targets for anabolic agents have been identified. New parathyroid hormone (PTH) and PTH-related protein (PTHrP) analogs remain under development. New anabolic targets being evaluated inhibit the Wnt-signaling pathway in osteoblasts (Fig. 1). Monoclonal antibodies to these targets block inhibition of the pathway, which leads to bone formation. Other therapeutic targets being investigated involve signaling pathways regulated by bone morphogenetic proteins, hedgehog proteins, and fibroblast growth factors.

3.1. PTH analogs

The only anabolic therapies currently approved to treat osteoporosis to date are recombinant forms of human PTH. Human recombinant PTH 1–34 (teriparatide) [11] and PTH 1–84 [12] have been approved in several countries to treat osteoporosis. Stopping treatment with these agents leads to rapid bone loss, so patients are usually switched to long-acting bisphosphonates or other agents to consolidate BMD gained during treatment [13].

PTH analogs are given by daily subcutaneous injection. Their most common side effects are mild asymptomatic hypercalciemia and hypercalciuria [11,12]. Teriparatide received a black box warning from the FDA because of concerns regarding osteosarcoma seen in the Fischer 344 rat in one preclinical study. There have been no human osteogenic sarcoma cases to date known to be caused by teriparatide or other PTH analogs [14]. PTH analogs are expensive to produce, and therefore cost significantly more than the other agents used to treat osteoporosis.

A recent study showed that teriparatide given by once weekly subcutaneous injection increased BMD effectively in humans [15]. Once monthly and once yearly administration of PTH fused to a collagen-binding domain was recently shown to extend its anabolic activity in mice [16,17]. The pharmacokinetic profile of a single dose of a novel oral PTH formulation has been evaluated in healthy postmenopausal women [18].

Because intermittent subcutaneous administration of PTH causes anabolic effects on bone, short-term intermittent antagonism of the parathyroid CaSR by calcilytic compounds might result in short bursts of endogenous PTH secretion. Ronacaleret, an oral CaSR antagonist, transiently stimulated PTH secretion, but the PTH release was prolonged enough to cause bone loss, similar to what is seen in primary hyperparathyroidism [19]. A preclinical study showed that JTT-305, another oral CaS antagonist, stimulated transient PTH secretion and new bone formation in ovariectomized rats [20].

3.2. PTH-related protein analogs

PTHrP was originally identified as the main cause of hypercalcemia of malignancy. Intermittent injection of recombinant analogs of PTHrP is being investigated to see if these might improve BMD and reduce fractures. Human recombinant PTHrP 1–34 was recently shown to have similar effects to teriparatide in a small clinical trial [21].

3.3. Activators of the Wnt/β-catenin signaling pathway

Binding of Wnt to its 7-transmembrane receptor and low density lipoprotein receptor-related protein 5 or 6 (LRP 5/6) in osteoblasts inhibits formation of intracellular glycogen synthase kinase-3 (GSK3) (Fig. 1). Inhibition of Wnt binding leads to increased GSK3, which prevents breakdown of β-catenin. Increased translocation of β-catenin to the nucleus causes transcriptional coactivation of genes integral to bone formation [22].

Several endogenous antagonists inhibit the Wnt/β-catenin pathway. Wnt-inhibitory factor and members of the secreted frizzled-related protein family downregulate the Wnt/β-catenin pathway and lead to decreased bone formation. LRPS/6 inhibitors such as sclerostin and Dickkopf-1 also downregulate this pathway.
Inhibitors of sclerostin and Dickkopf-1 are known to stimulate bone formation. Anti-sclerostin monoclonal antibody stimulated bone formation and increased BMD and bone strength in a rat preclinical study [23]. A randomized, placebo-controlled phase I study in 72 healthy adults showed that a single subcutaneous dose of anti-sclerostin antibody (AMG 785) increased BMD [24]. A range of subcutaneous doses from 0.1 to 10 mg/kg were studied in 56 subjects, with intravenous doses of 1 or 5 mg/kg studied in 16 subjects. A single dose of AMG 785 by either the subcutaneous or intravenous route caused a dose-dependent increase in markers of bone formation, and a dose-dependent decrease in a marker of bone resorption. A dose-dependent increase in BMD was seen as early as one month after administration. The largest BMD increases seen were 5.3% at the lumbar spine, and 2.8% at the total hip, on day 85 after the single 10 mg/kg subcutaneous dose. This agent was well tolerated at all doses. All adverse events were mild, except for one subject who received the 10 mg/kg dose, who developed severe non-specific hepatitis. Liver enzymes increased the first day after dosing, but normalized by day 26.

A monoclonal antibody to Dickkopf-1 (RH2-18) is being developed. RH2-18 given subcutaneously to ovariectomized mice and rhesus macaques increased BMD, especially trabecular BMD [25]. Eight weeks of weekly injections of RH2-18 in ovariectomized mice increased femoral BMD to the level of controls without ovariectomy, and partially restored lumbar spine BMD toward that of controls. RH2-18 given every two weeks for 9 months increased lumbar spine BMD by 5.0%.

3.4. Other anabolic agents

Other novel targets are currently being evaluated in preclinical studies. Potential targets include growth factors, such as bone morphogenetic proteins (BMPs), transforming growth factor-β (TGF-β), growth hormone, and insulin-like growth factor-1 (IGF-1). Recombinant human BMP-2 has been used locally in patients with bisphosphonate-associated jaw osteonecrosis, and found to stimulate bone formation sufficiently to heal these difficult to treat lesions [26]. Statins and statin-like molecules have been shown to stimulate BMP-2 gene expression and vascular endothelial growth factor (VEGF) expression in osteoblasts, and to stimulate fracture healing in animals [27]. There have been no randomized controlled trials in humans evaluating the use of these agents for the treatment of osteoporosis.
4. Conclusion

Treatment of osteoporosis has advanced significantly beyond hormone therapy administered at menopause. For patients not able to take hormone therapy, bisphosphonates, raloxifene, calcitriol, denosumab, and teriparatide have been excellent options that effectively reduce fracture risk. The new therapeutic targets described in this mini-review will further expand the options available to physicians and their patients for the treatment of osteoporosis.

Practice points

- Until the new anabolic or antiresorptive agents become available, physicians should continue to recommend the current best agent uniquely suited for each patient.
- Use of currently available agents should not preclude the use of new agents when these become available.
- Physicians and patients should be aware that, unlike the longer-acting bisphosphonates, all the new agents are short-acting, and have rapid offset of action.
- Physicians should consider starting longer acting bisphosphonates once treatment with new short-acting agents is completed.

Research agenda

- Continue clinical trials of currently available new antiresorptive and anabolic agents.
- Continue development of new therapeutic agents currently undergoing preclinical study.
- Continue research on agents targeting anabolic pathways other than the Wnt/β-catenin signaling pathway to expand options for treatment.

Contributors

Both authors contributed equally to the design, writing, and editing of this mini-review, submitted at the invitation of the Editor-in-Chief, Dr. Margaret Rees.

Competing interests

Neither author has any competing interests to declare.

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