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Review article

New treatments of osteoporosis

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Abstract

Osteoporosis is characterized by low bone mass, deteriorated bone architecture and increased risk of is fractures. The current available treatments of osteoporosis comprise antiresorptive and anabolic treatments. Bisphosphonates and RANKL antibody are the most widely used antiresorptive treatments while teriparatide is the only available anabolic treatment of osteoporosis. A common feature of antiresorptive as well as anabolic treatment is that bone resorption and formation remain coupled. Both types of treatment therefore establish a period of positive balance but because of the coupling, this period is temporary.

The focus of this review is two new classes of anti-osteoporosis treatments; inhibition of cathepsin K and inhibition of sclerostin. Through very different mechanisms of action both may prove capable of uncoupling resorption and formation. Cathepsin K is a lysosomal cysteine protease that degrades bone matrix proteins including collagen type I. Animal and human studies have demonstrated that inhibition of cathepsin K leads to increased bone mass across species and reduced fracture risk in postmenopausal women.

Sclerostin activates the Wnt canonical pathway and stimulates bone formation through stimulation of osteoblast differentiation, proliferation and survival. Short-term studies of antibody mediated inhibition of sclerostin in animals and postmenopausal women have consistently shown stimulation of bone formation and reduced or unaltered bone resorption. Clinical studies in postmenopausal women have shown increases in bone mass.

If these two new treatments demonstrate anti-fracture efficacy at the same level or better as the best of the currently approved treatments, they will become valuable tools for improving the treatment of osteoporosis.

Keywords: Osteoporosis; Antiresorptive; Anabolic; Cathepsin K; Sclerostin

1. Introduction

Osteoporosis is characterized by low bone mass and deteriorated bone architecture [1,2]. Osteoporosis is common, affecting one in three postmenopausal women and one in five men, corresponding to 200 million women and men, worldwide [3]. The immediate clinical consequence of osteoporosis is fracture [4,5]. Furthermore, osteoporotic fractures, vertebral as well as hip are associated with morbidity and increased mortality [6–8].

Care of patients with osteoporosis has improved significantly over the last 2–3 decades. The WHO definition of osteoporosis based on a bone mineral density (BMD) T-score <−2.5 made it possible to identify individuals at risk of fracture before the first fracture [2]. FRAX™ and other similar tools available for estimating future risk of fractures have made it possible to further direct treatment to the patients at the highest risk of fracture [9,10]. Several pharmacological treatments have been developed and approved for clinical use. Although this in principle should have lead to a personalized approach to treatment, the choice of treatment is in many countries restricted to the cheapest treatment. Other treatments are only reimbursed if the first treatment has failed.

Optimal management of osteoporosis is also confronted with other challenges. Patients with fractures due to osteoporosis are treated by orthopedic surgeons who are primarily focused on fracture treatment and not on the prevention of the next fracture. Patients with fractures are therefore not

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routinely investigated for osteoporosis and the need for an intervention that may prevent the next fracture. The gap in the management of osteoporosis has been recognized and it has been demonstrated that the most efficient way to overcome this gap is by organizing a "fracture liaison service" where dedicated personnel are responsible for guiding the patient from the orthopedic department, through DXA and other investigations back to the general practitioner who in the end is responsible for treatment and follow-up [11,12].

Other challenges comprise patients who do not respond to existing treatments and patients or physicians stopping treatment prematurely due to fear of long-term adverse effects of existing therapies.

The current available treatments of osteoporosis comprise antiresorptive and anabolic treatments. The antiresorptive treatments are bisphosphonates, receptor activator of nuclear factor kappa-B ligand (RANKL) antibody, and selective estrogen receptor modulators (SERM) [13]. They have different mechanisms of action, but in the end they all inhibit osteoclast function. Bisphosphonates and RANKL antibody are the most widely used antiresorptive treatments. They are both generally well tolerated, but osteonecrosis of the jaw and atypical femur fractures are very rare side effects that have gained much attention and are causing much concern [14,15].

Teriparatide (PTH1-34) is currently the only available anabolic treatment of osteoporosis. Patients generally respond well to teriparatide with impressive increases in bone mass [16]. However, some patients are still left with a very low bone mass after teriparatide treatment and in some of these patients fractures cannot in a longer perspective be prevented by the available antiresorptive treatments. It would therefore be desirable to have the option of a second period of anabolic treatment. This is currently not possible with teriparatide.

Bone modeling is the process by which bone grow and adapt its shape accordingly during childhood, adolescence and young adulthood. Bone remodeling is the process by which old bone is replaced by new bone. The remodeling process is characterized by five phases: Activation, resorption, reversal, formation and resting, which are coupled in location and time. Bone loss and osteoporosis are caused by a negative balance between the amount of resorbed and subsequently formed bone [17]. A common feature for the available treatments, antiresorptive as well as anabolic is that bone resorption and bone formation remain coupled. Existing antiresorptive treatments suppress bone resorption and second to this bone formation is also suppressed. The anabolic treatment available; teriparatide stimulates bone formation and as a consequence of this bone resorption is also stimulated. Both types of treatment therefore establish a period of positive balance between bone formation and bone resorption, but because of the coupling, this period is only temporary. It has been speculated that this could be the explanation for the relatively limited effect of existing treatments on the prevention of non-vertebral fractures [18]. The mechanisms underlying fragility at cortical and cancellous bone compartments are different. In cancellous bone, fragility is associated with remodeling activity, as a resorption cavity with its temporary thinning of the trabeculae has been demonstrated to be a stress-riser with increased risk of collapse of the trabeculae and subsequent loss of trabecular connectivity. Due to the negative remodeling balance in postmenopausal women and elderly men, remodeling itself and especially increased remodeling activity convey a risk of loss of trabeculae due to thinning of the trabeculae and therefore the risk of a resorption lacunae penetrating the trabeculae or due to two resorption lacunae on each side of a trabeculae merging. The fragile situation in cancellous bone can relatively quickly be restored by antisorptives, because bone remodeling is significantly reduced [19] and by teriparatide, because trabeculae are becoming thicker [20]. The situation in cortical bone is different. Fragility of cortical bone is associated with thinning of the cortex and increased porosity. Both are caused by increased remodeling activity. Bisphosphonates have demonstrated limited ability to improve hip BMD and it has been suggested that this is due to limited access to cortical bone [21]. Denosumab has been demonstrated to be potentially more active at the cortical department, perhaps due to better access [22]. Denosumab has been demonstrated to reduce cortical porosity and continuously increase hip BMD over many years [23], still the prevention of non-vertebral fractures is not optimal. Teriparatide is able to stimulate endocortical bone formation, but subsequently stimulates cortical remodeling, leading to increased porosity and decreasing cortical volumetric BMD [24,25]. Because of these build in limitations of the available treatments of osteoporosis, there is a need for treatments that are capable of uncoupling bone resorption and formation. Attempts have been made of combining existing antiresorptives with teriparatide and additive effects have been shown on BMD despite very different patterns of changes in biochemical markers of bone turnover [26,27]. None of these studies investigated if these regiments improved fracture prevention.

The focus of this review will be two new classes of anti-osteoporosis treatments; inhibition of cathepsin K and inhibition of sclerostin. Both may prove to be able to uncouple resorption and formation, although through very different mechanisms of action.

2. Inhibition of cathepsin K

2.1. Cathepsin K

Resorbing osteoclasts adhere very tightly to the bone surface and seal off the resorption lacunae. The osteoclasts generate an acidic environment in the lacunae by secreting protons. Bone mineral is dissolved by the acidic environment and the collagen and other non-collagenous proteins are degraded by proteases. Cathepsin K is one of these proteases, others include metalloproteinases. Cathepsin K is a lysosomal cysteine protease that degrades bone matrix proteins including collagen type I [28]. Cathepsin K is predominantly, but not exclusively expressed in osteoclasts and is stored in lysosomes until it is released into the resorption cavity, where it is activated by the acidic environment.