Available online at www.sciencedirect.com

ScienceDirect

Current Opinion in Pharmacology

New horizons in osteoporosis therapies

Torben Harsløf and Bente L Langdahl

Efficient therapies are available for the treatment of osteoporosis, however, there are still unmet needs. Anti-resorptive therapies only increase bone mineral density to a certain extent and reduce the risk of non-vertebral fractures by 20%, only one anabolic option is available — the effect of which levels off over time, and the evidence for combination therapy targeting both resorption and formation is limited. The current review will focus on emerging treatments of osteoporosis with the potential of enhanced anabolic effects (romosozumab and abaloparatide) or uncoupling of resorption and formation (odanacatib and romosozumab) as well as the effect of combination therapy.

Address
Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Tage-Hansens Gade 2, 8000 Aarhus C, Denmark

Corresponding author: Langdahl, Bente L (bente.langdahl@aarhus.rm.dk)

Current Opinion in Pharmacology 2016, **28**:38–42

This review comes from a themed issue on **Musculoskeletal**

Edited by **Isabel R Orriss** and **Vicky E MacRae**

http://dx.doi.org/10.1016/j.coph.2016.02.012

Introduction

Osteoporosis affects more that 200 million patients worldwide [1]. Osteoporosis increases fracture risk [2] and in particular fractures of the hip and spine increase mortality [3,4]. Bone is remodeled throughout life during a process where old bone is resorbed by osteoclasts that subsequently stimulate formation of new bone by osteoblasts [5]. This makes osteoclasts and osteoblasts obvious targets for pharmaceutical intervention and the currently available osteoporosis treatments are either anti-resorptive (inhibiting the osteoclasts) or anabolic (stimulating the osteoblasts) [6]. The anti-resorptive treatments are bisphosphonates, receptor activator of nuclear factor kappa-B ligand (RANKL) antibody, and selective estrogen receptor modulators (SERM) that either cause osteoclast apoptosis (bisphosphonates) or inhibit osteoclast recruitment (RANKL-antibodies and SERM). Teriparatide (PTH1-34) is the only anabolic treatment [6].

The Achilles heel of the current treatments is that bone resorption and formation remain coupled which from a pharmacological and clinical point of view results in unmet needs. First, anti-resorptive treatments can only increase bone mineral density (BMD) to a certain extent as the decrease in osteoclast number subsequently prevents de novo synthesis of new bone by osteoblasts. Second, teriparatide stimulates osteoblasts and subsequently osteoclasts which limits the effect and some patients with very low bone mass or suboptimal response to teriparatide are left with very low BMD after treatment. Third, only few studies have examined if this coupling can be overcome and the unmet needs may be improved by combining the therapies. The current review will focus on emerging osteoporosis treatments that may overcome these needs as well as outline the evidence for combination therapy. The main effects of the drugs covered in this review are summarized in Table 1.

Cathepsin K inhibition

During resorption osteoclasts seal off the resorption lacuna and generate an acidic environment into which proteases are excreted to degrade collagen and non-collagenous proteins of bone. One of these proteases is cathepsin K that is predominantly expressed in osteoclasts [7]. Odanacatib is a reversible inhibitor of cathepsin K [8]. Odanacatib interferes only with osteoclast *activity* but not osteoclast *viability* and the osteoclasts are therefore still able to activate osteoblasts. This provides odanacatib with the potential of uncoupling bone resorption and formation. A number of phase II trials have investigated the effects of odanacatib. A global trial comprising 399 postmenopausal women compared four doses of odanacatib (3, 10, 25, and 50 mg weekly) to placebo over 2 years [9]. The bone resorption marker u-crosslinked N-terminal telopeptide of type 1 collagen/creatinine (uNTx/Cr) was dose-dependently decreased by 60% and 52% after 12 and 24 months, respectively, in women treated with odanacatib 50 mg weekly. In a Japanese study comprising 287 men and women [10] and in a male study comprising 292 Caucasian men [11] a similar level of suppression was seen. Regarding bone formation markers, however, different results were seen. In the global study and the male study s-procollagen type I N-terminal propeptide (sPINP) dose-dependently decreased during the first 6 months by approximately 40% and thereafter gradually returned towards baseline levels [9,11]. In the Japanese study sPINP decreased by approximately 50% at month 6 and remained at this level for the rest of the study period [10]. Thus the effect on bone resorption markers appears to be consistent across different populations whereas the effect on formation markers varies. Bone biopsies were obtained in the global phase 2 as well as in a special imaging study [9]. The biopsies

Table 1

Summary of the main effects seen in clinical trials on bone mineral density (BMD) and fracture risk reduction of the drugs covered in this review

Treatment	Drug class	Pharmacodynamics	Increase in BMD	Fracture risk reduction
Odanacatib	Antiresorptive	Inhibition of cathepsin K that is a protease from osteoclasts	lsBMD 11.2%[a] fnBMD 9.5%[a]	Hip 47%[a] Non-vertebral 23%[a] Clinical vertebral 72%[a]
Romosozumab	Anabolic	Inhibition of sclerostin that inhibits the osteoblast	lsBMD 11.3%[b] thBMD 4.1%[b]	NA
Abaloparatide	Anabolic	Intermittent activation of the PTH type 1 receptor and thereby activation of osteoblasts	lsBMD 6.7%[c] thBMD 2.6%[c]	Major osteoporotic 67%[d]
Combination therapy	Anabolic and antiresorptive	Inhibition of RANKL and thereby recruitment of osteoclasts (denosumab) and short-term activation of the PTH type 1 receptor and thereby activation of osteoblasts (teriparatide)	lsBMD 12.9%[e] thBMD 6.3%[e]	NA

lsBMD: lumbar spine BMD, fnBMD: femoral neck BMD, thBMD: total hip BMD, NA: data not available.
[a] Odanacatib 50 mg weekly for 5 years [13••].
[b] Romosozumab 210 mg monthly for 12 months [20••].
[c] Abaloparatide 80 μg daily for 24 weeks [32].
[d] Abaloparatide 80 μg daily for 18 months [33••].
[e] Denosumab 60 mg every 6 months in combination with teriparatide 20 μg daily for 24 months [40••].

showed no major effects on activation frequency or bone formation which is in accordance with animal studies demonstrating unchanged number of resorption lacunae in response to cathepsin K inhibition but that these are shallow [12].

In the phase III trial (The Long-term Odanacatib Fracture Trial, LOFT) comprising 16,713 postmenopausal women, the patients received odanacatib 50 mg weekly or placebo. Odanacatib increased BMD at the lumbar spine and total hip after 5 years by 11.2 and 9.5%, respectively and reduced the risk of hip fractures by 47%, the risk of non-vertebral fractures by 23%, the risk of clinical vertebral fractures by 72%, and the risk of new/worsening morphometric vertebral fractures by 54% [13••]. These reductions in fracture risk are comparable to those seen with the bisphosphonates alendronate and zoledronic acid as well as the RANKL antibody denosumab [14–16].

In conclusion, odanacatib is a potential new antiresorptive treatment of osteoporosis with an anti-fracture efficacy comparable to current treatments. The drug still awaits approval by the medical authorities.

Sclerostin inhibition

Bone formation by the osteoblasts can be stimulated via the canonical Wnt-pathway in which lipoprotein related peptide (LRP) 5 and -6 binds to the frizzled receptor and promotes bone formation [17]. The osteocytes are terminally differentiated osteoblasts that are imbedded within bone matrix and control bone formation by producing sclerostin that prevents the binding of LRP5 and-6 to the frizzled receptor and thereby *inhibits* bone formation [18].

Romosozumab is an antibody against sclerostin that has demonstrated bone forming potential [19]. The effect of romosozumab on bone turn-over and BMD has been investigated in women in a phase II trial. The women were randomized to 12 months treatment with one of five different doses of romosozumab either monthly or three-monthly, alendronate 70 mg weekly, teriparatide 20 mg daily, or placebo [20••]. Treatment with romosozumab 210 mg monthly increased sPINP by 91% after 1 month but the increase leveled off over the following months and at the end of the treatment period sPINP was 20% below baseline level. In addition the bone resorption marker s-C-terminal telopeptide (sCTx) decreased by 41% one week after administration of the first dose of romosozumab and then slightly increased to a level 26% below baseline at 12 months. Thus, romosozumab appears to not only stimulate formation but also to inhibit resorption. The fact that formation is decreased after twelve months is somewhat surprising but it has been suggested to be caused by depletion of osteoblast progenitors or a compensatory increase in other inhibitors of bone formation such as dickkopf [21•]. The suppression of bone resorption is most likely caused by a reduction in the osteocyte production of RANKL due to the inhibition of sclerostin [22]. Finally, romosozumab 210 mg monthly increased lumbar spine BMD 11.3% which was significantly more than teriparatide, alendronate, and placebo that increased lumbar spine BMD by7.1%, 4.1%, and 0.1% respectively. A similar pattern was seen at the total hip where BMD changed by 4.1%, 1.3%, 1.9% and -0.7% in women treated with romosozumab, teriparatide, alendronate, or placebo, respectively [20••]. The study was extended and by the end of the second year romosozumab