

Therapy of Osteoporosis

Salvatore Minisola and Elisabetta Romagnoli

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Abstract

The goal of any osteoporosis therapy is the prevention of both vertebral and nonvertebral fractures, which in principle can be achieved by inhibiting bone resorption and/or by stimulating bone formation. There are currently several osteoporosis treatment options that may be suitable for various patient populations, including oral and IV bisphosphonates, SERMs, calcitonin, teriparatide, strontium ranelate, and denosumab. The choice of osteoporosis therapy should be individualized based on consideration of the efficacy, safety, cost, convenience (i.e., dosing regimen and delivery), and other non-osteoporosis-related benefits associated with each agent. Given the limitations of current antiosteoporosis drugs, a search for new therapeutics has focused in the last few years on also identifying novel antiresorptives that prevent the decrease in activation frequency and bone formation and on bone anabolics that increase bone formation directly without affecting bone resorption. It will be important to incorporate new and emerging agents into this individualized treatment paradigm to optimize clinical outcomes in patients with osteoporosis.

1 Introduction

Osteoporosis is a systemic skeletal disease characterized by an unbalanced and/or uncoupled bone-remodeling activity leading to bone loss, microarchitectural deterioration of bone, and ultimately fractures at typical sites such as the lumbar spine, the femoral neck, and the distal radius. These fractures are often associated with an increase in morbidity, disability, and mortality, particularly in the elderly. Because of its widespread nature, with a 50 % fracture risk in all women after the age of 50 years and a 25 % risk in men, osteoporosis is a global public health concern and a great socioeconomic burden (Cauley et al. 2000; MacLean et al. 2008; Bolland et al. 2010; Harvey et al. 2010).

S. Minisola (✉) · E. Romagnoli
Department of Internal Medicine and Medical Disciplines,
University of Rome “Sapienza”, Viale del Policlinico 155,
00161 Rome, Italy
e-mail: salvatore.minisola@fastwebnet.it

The goal of any osteoporosis therapy is the prevention of both vertebral and nonvertebral fractures, which in principle can be achieved by inhibiting bone resorption and/or by stimulating bone formation. Effective osteoporosis treatment can significantly reduce vertebral and nonvertebral fractures rate and mortality (MacLean et al. 2008; Bolland et al. 2010). On the contrary, untreated osteoporosis was associated with significant increase in hospitalization and costs for medical care (Lindsay et al. 2001; Huybrechts et al. 2006). However, despite the increasing burden of osteoporosis on a global scale, a vast number of individuals at high risk of fracture remain undiagnosed or untreated.

The World Health Organization (WHO)-defined bone mineral density (BMD) T-score of ≤ 2.5 standard deviation is frequently used as both a diagnostic and intervention threshold for osteoporosis (McCloskey 2010). However, the majority of osteoporotic fractures has been shown to occur in individuals with BMD values above the osteoporosis threshold, typically in the osteopenic range (T-score of less than -1 and greater than -2.5) (Siris et al. 2001). The WHO has developed the Fracture Risk Assessment Tool (FRAX®) (Kanis et al. 2009), which calculates the 10-year probability of a major osteoporotic fracture. Risk factors for osteoporotic fracture, according to the FRAX® algorithm, include prior fragility fracture, parental history of hip fracture, current tobacco smoking, use of oral glucocorticoids, rheumatoid arthritis, other causes of secondary osteoporosis, and alcohol consumption of three or more units daily (Kanis et al. 2008). Guidelines originally published in 2008 and updated in 2010 by the National Osteoporosis Foundation (NOF) recommend osteoporosis treatment in postmenopausal women or men aged 50 years and older with a T-score of -2.5 or lower at the femoral neck, hip, or spine or with a prior hip or spine fracture; treatment is also indicated for patients with low bone mass (T-score between -1.0 and -2.5) and a 10-year probability of hip fracture of $\geq 3\%$ or a 10-year probability of major osteoporosis-related fracture of $\geq 20\%$, as determined by FRAX® (National Osteoporosis Foundation 2010).

The choice of osteoporosis therapy should be individualized based on consideration of the efficacy, safety, cost, convenience (i.e., dosing regimen and delivery), and other non-osteoporosis-related benefits associated with each agent (Laroche 2008; Silverman and Christiansen 2012). Daily supplementation with calcium and vitamin D is recommended as a baseline therapy as part of most pharmacologic regimens (National Osteoporosis Foundation 2010). For some women, lifestyle changes alone, including increased calcium and vitamin D intake, exercise, and fall prevention, may be sufficient to reduce the risk of osteoporosis.

Pharmacological treatments for osteoporosis can be divided into two categories: antiresorptive agents and anabolic agents. Antiresorptive drugs suppress bone resorption

and are the most commonly agents used for treatment of osteoporosis. Anabolic agents rather stimulate bone formation, thus increasing bone mass and represent a more recent therapeutic approach for osteoporosis treatment.

Given the limitations of current antiosteoporosis drugs, a search for new therapeutics has focused in the last few years on also identifying novel antiresorptives that prevent the decrease in activation frequency and bone formation and on bone anabolics that increase bone formation directly without affecting bone resorption. This chapter summarizes the current status of pharmacological treatment of postmenopausal osteoporosis and the major evidences concerning old and new drugs.

2 Antiresorptive Drugs

2.1 Estrogens

Estrogens represent the oldest antiresorptive therapy recognized to be effective for the prevention of early postmenopausal bone loss and fracture (Riggs et al. 2002; Rossouw et al. 2002; Khosla 2010). However, the use of these agents was largely discouraged by the well-known increased risk of breast and endometrial cancer, cardiovascular disease, and dementia (Riggs et al. 2002; Rossouw et al. 2002). Physiologically, estrogens play a major role in the acquisition of bone mass during growth and pregnancy and have important effects on extraskelatal calcium homeostasis (Heshmati et al. 2002; Riggs et al. 2002). Indeed, estrogens stimulate osteoclast apoptosis and suppress osteoblast and osteocyte apoptosis (Riggs et al. 2002). Estrogen deficiency is also associated with an increased lifespan of osteoclasts and a reduction in osteoblasts lifespan, as well as with a raise in proresorptive cytokines, that lead to a significant bone loss and enhanced mobilization of calcium from the skeleton (Khosla 2010). Some evidences suggested that even the low serum estrogen levels in late postmenopausal women could have beneficial effects on bone (Heshmati et al. 2002). However, large-scale studies on fractures preventions and safety profile associated with estrogen low-dose treatment are still lacking (Khosla 2010).

Current clinical recommendations state that hormone replacement therapy should be used for treatment of menopausal symptoms for the shortest period of time and as osteoporosis therapy after consideration of all other treatments and of all patients' risks and benefits (Rossouw et al. 2002).

2.2 SERMS

Selective estrogen receptor modulators (SERMS) have been developed in order to provide the beneficial effects of

estrogens on bone without adverse effects on other tissues. Indeed, SERMS act on estrogens receptor with a tissue-specific mechanism, thus acting as estrogen antagonist on brain and breast and as agonist on bone (Khosla 2010). The only SERMS currently utilized for the treatment of postmenopausal osteoporosis are raloxifene and bazedoxifene.

2.2.1 Raloxifene

Raloxifene is approved for treatment of osteoporosis at the oral dose of 60 mg once-daily. A meta-analysis of seven randomized, double-blind, placebo-controlled trials demonstrated a reduced vertebral fractures risk in postmenopausal women with osteoporosis, but no efficacy was reported for nonvertebral and hip fractures (Rossouw et al. 2002; Seeman et al. 2006). A reduced risk of developing breast cancer was also reported with raloxifene (Khosla 2010). However, raloxifene can increase the risk of venous thromboembolic disease, fatal stroke, and menopausal symptoms (Rossouw et al. 2002; Khosla 2010).

2.2.2 Bazedoxifene

Bazedoxifene is a novel SERM that was recently approved in the European Union for the treatment of osteoporosis in postmenopausal women at high risk of fracture. In a 3-year phase 3 study, bazedoxifene 20 and 40 mg/day significantly reduced the risk of new vertebral fracture by 42 and 37 % relative to placebo, respectively, in postmenopausal women with osteoporosis (Silverman et al. 2008). The incidence of nonvertebral fractures was not significantly different among bazedoxifene, raloxifene, and placebo groups. The results were confirmed in a 2-year extension of the 3-year treatment study that evaluated the longer term efficacy and safety of bazedoxifene in women with postmenopausal osteoporosis (Silverman et al. 2012).

2.3 Bisphosphonates

The introduction of bisphosphonates in clinical practice almost two decades ago was a major advance in the management of postmenopausal osteoporosis. Because of their antifracture efficacy and generally good tolerability, bisphosphonates rapidly became and still remain the mainstay of therapy for postmenopausal osteoporosis (Eastell et al. 2011).

Bisphosphonates are effective in reducing bone turnover, increasing BMD and reducing fracture risk in postmenopausal women with osteoporosis. Their efficacy is based on their ability to restore the rate of bone turnover to premenopausal levels, thereby preventing further deterioration of bone quality in patients with accelerated bone loss. The licensed bisphosphonates exhibit some differences in potency and speed of onset and offset of action. These differences

mean that different agents may be more advantageous in different situations.

These drugs are derivatives of inorganic pyrophosphate and bind to hydroxyapatite crystals in the skeleton (Eastell et al. 2011). Thus, they have a long half-life in the skeleton and are preferentially incorporated and accumulated at sites of accelerated bone turnover, where they act as inhibitors of osteoclast-mediated bone resorption (Favus 2010). Second- and third-generation bisphosphonates have nitrogen-containing side chains and are the agents actually most commonly used for osteoporosis treatment. In Europe the bisphosphonates approved for the treatment and prevention of osteoporosis are: alendronate, risedronate, and ibandronate, given by os, and intravenous ibandronate and zoledronic acid (Russell 2011).

2.3.1 Alendronate

Alendronate is an aminobisphosphonate used for the treatment of postmenopausal osteoporosis nowadays almost exclusively at 70 mg once-weekly oral regimen. The Fracture Intervention Trial (FIT) showed a significant reduction of vertebral fractures in patients with ≥ 1 vertebral fracture at baseline receiving alendronate for 3 years, and among patients without vertebral fractures at baseline after 4 years of alendronate (Black et al. 1996; Cummings et al. 1998; Bilezikian 2009). A meta-analysis of the combined non-vertebral fractures data from five prospective, randomized, placebo-controlled trials of at least 2 years' duration, found that alendronate significantly reduced the risk of nonvertebral fractures in postmenopausal women with osteoporosis (Karpf et al. 1997). The Fracture Intervention Trial Long-term Extension (FLEX) study evaluated the effects of continuation or discontinuation of alendronate for an additional 5 years (after the first 5 years of therapy) and showed a reduced risk for clinical vertebral fractures, but not for nonvertebral and morphometric vertebral fractures in women receiving alendronate (Black et al. 2006).

2.3.2 Risedronate

Risedronate is a third generation bisphosphonate used for the treatment of osteoporosis nowadays almost exclusively as 35-mg weekly and 75-mg for 2 consecutive days to the month oral dose. VERT-NA and VERT-MN trials showed that risedronate significantly reduced vertebral and non-vertebral fractures and increased BMD at both lumbar spine and femoral neck after 3 years of therapy, compared to placebo, in women with previous vertebral fractures (Harris et al. 1999; Bilezikian 2009). VERT-MN Extension Trial confirmed these results at 5 years (Harris et al. 1999; Sorensen et al. 2003). The Hip Intervention Program trial reported a reduction in the risk of hip fracture in elderly women with confirmed osteoporosis but not in elderly

women with risk factors for osteoporosis other than low BMD after 3 years of risedronate (McClung et al. 2001).

2.3.3 Ibandronate

Ibandronate is a potent nitrogen-containing bisphosphonate administered intermittently at the oral dose of 150 mg once-monthly and as intravenous injections of 3 mg every 3 months. The BONE study reported a reduction in new morphometric and clinical vertebral fractures, but not nonvertebral fractures, in women with postmenopausal osteoporosis treated with oral ibandronate (Chesnut et al. 2004). Moreover, subsequent studies showed that the 150 mg once-monthly oral dose and intravenous 3 mg, administered every 3 months, are more efficacious than the daily oral regimen of 2.5 mg (Reginster et al. 2006; Eisman et al. 2008).

2.3.4 Zoledronic Acid

Zoledronic acid represents the most potent aminobisphosphonate and is approved for the treatment of osteoporosis as a single 15-min infusion at the dosage of 5 mg every 12 months. The HORIZON Pivotal Fracture Trial reported a significant decrease in morphometric and clinical vertebral fractures, hip fractures, nonvertebral fractures, and clinical fractures among postmenopausal women 65–89 years of age treated with once-yearly zoledronic acid infusions over 3 years, compared to placebo (Black et al. 2007). To assess the effect of zoledronate beyond 3 years, an extension study of the HORIZON-PFT in which women on zoledronate for 3 years were randomly assigned to zoledronate or placebo for 3 more years was conducted. Small differences in bone density and markers in those who continued versus those who stopped treatment suggest residual effects, and therefore, after 3 years of annual zoledronate, many patients may discontinue therapy up to 3 years. However, vertebral fracture reductions suggest that those at high fracture risk, particularly vertebral fracture, may benefit by continued treatment (Black et al. 2012).

2.3.5 Safety

Upper gastrointestinal adverse effects represent the most common cause of patients' intolerance and discontinuation of oral bisphosphonates and include nausea, dyspepsia, abdominal pain, gastritis, and other non-specific symptoms. Accordingly, in clinical practice, patients should take these drugs fasting with a full glass of water and maintain an upright posture for at least 30 min after ingestion. Indeed, suboptimal administration of medication is considered the main cause of the erosive oral bisphosphonates-associated esophagitis (Kennel and Drake 2009).

A transient acute phase reaction has been associated with IV bisphosphonates injection, with the higher incidence after the first administration. A flu-like syndrome is the most

common clinical presentation, with fever, myalgias, and arthralgias that resolves within 24–72 h and could be ameliorated by anti-inflammatory drugs (Kennel and Drake 2009).

Transient hypocalcemia is a well-recognized effect of IV bisphosphonates injection, particularly in patients with hypoparathyroidism, renal failure, hypovitaminosis D, or in the elderly. Thus, a correct supplementation with calcium and vitamin D in patients which would receive IV bisphosphonates is strongly recommended (Kennel and Drake 2009).

Bisphosphonate-associated osteonecrosis of the jaw is defined as an area of exposed bone in the maxillofacial region that did not heal within 8 weeks in a patient exposed to a bisphosphonate and had not had radiation therapy to the craniofacial region (Khosla et al. 2007). The incidence is relatively low in patients receiving oral bisphosphonates for osteoporosis and considerably higher in patients with malignancy receiving high doses of intravenous bisphosphonates (Khosla et al. 2007). However, a careful oral examination for active or anticipated dental issues and a good oral hygiene are highly recommended (Khosla et al. 2007). Safety concerns associated with the long-term use of bisphosphonates include atypical fractures, such as low-impact subtrochanteric stress fractures or completed fractures of the femur. It has been suggested that in some patients, prolonged administration of bisphosphonates may lead to over-suppression of bone turnover, which no longer permits remodeling to repair microdamage and thereby reduces bone strength. However, the absolute risk of atypical fracture associated with bisphosphonates for the individual patient with a high risk of osteoporotic fractures is small compared with the beneficial effects of the drug (Shane et al. 2010).

Bisphosphonates should not be used in patients with active gastrointestinal symptoms, delayed esophageal emptying, or other esophageal pathology and creatinine clearance less than 30–35 ml/min. However, some post hoc analysis of trials with risedronate reported no difference in the incidence of adverse events in the treatment group regardless of renal function, compared to placebo (Watts and Diab 2010).

2.4 Denosumab

Denosumab is a fully human monoclonal antibody that specifically binds to the receptor activator of nuclear factor- κ B ligand (RANKL), thus blocking its interaction with its receptor, RANK, on osteoclasts. This system is essential for the formation, function, and survival of osteoclasts (McClung et al. 2006; Cummings et al. 2009). Hence, denosumab acts as an inhibitor of osteoclasts-mediated bone resorption. The FREEDOM trial reported a reduction in vertebral and non-vertebral fractures, compared to placebo, in postmenopausal women with osteoporosis treated with 60 mg of denosumab

every 6 months for 36 months. Moreover, an increase in BMD at both lumbar spine and hip was reported; the drug is also associated with an increase in forearm BMD, suggesting a unique effect on cortical bone (Cummings et al. 2009). The pivotal trial also showed significant reductions in markers of bone turnover, C-telopeptide, and intact serum procollagen type I N-terminal propeptide, over 3 years (Cummings et al. 2009). Reductions in bone turnover were sustained over 4 and 6 years in open-label study extensions (Miller et al. 2011; Papapoulos et al. 2012).

The drug does not require renal clearance, and may be given to patients with renal impairment without dose adjustment, though with careful calcium supplementation because these patients are at higher risk of worsening hypocalcemia. There is some concern that treatment with denosumab may cause significant suppression of bone remodeling, the long-term effects of which are unknown. Adverse effects reported were: eczema, flatulence, cellulitis (including erysipelas), urinary tract and upper respiratory tract infection, constipation, arthralgia (McClung et al. 2006; Cummings et al. 2009).

Denosumab has been approved in Europe for the treatment of postmenopausal osteoporosis as a 60 mg subcutaneous injection every 6 months.

3 Anabolic Drugs

Anabolic drugs stimulate processes and mechanisms associated with bone formation, which is ultimately improved, leading to an increase in bone mass. Moreover, these agents affect a number of skeletal properties besides bone density, such as bone sizes and microarchitecture. The only anabolic therapy currently approved for osteoporosis treatment is the recombinant human parathyroid hormone (PTH).

3.1 Parathyroid Hormone (PTH)

Unlike chronic and continuous secretion of PTH that has a catabolic action on bone, the intermittent administration of low doses of PTH has potent anabolic effects on the skeleton. Indeed, PTH produces a prominent increment of BMD at both lumbar spine and femur and significantly decreases the incidence of vertebral and nonvertebral fractures, by stimulating bone formation and subsequently stimulates both bone formation and resorption (Neer et al. 2001; Canalis et al. 2007). Moreover, positive effects on bone connectivity, bone microarchitecture, and biomechanical properties of bone have been reported (Canalis et al. 2007). Two bioactive forms of PTH are currently available in Europe for osteoporosis treatment: teriparatide, the 1–34 fragments of PTH, and PTH (1–84), the intact human

recombinant molecule. Both the forms are administrated as a daily subcutaneous injection over a period of 24 months.

PTH is indicated in women and men at high risk of osteoporosis-related fractures, including those with vertebral or other osteoporosis-related fractures with BMD in the osteoporosis range, or very low BMD even in the absence of fractures (T-score < −3) and including individuals who have had an incident fracture or a bone loss during therapy with bisphosphonates agents (Canalis et al. 2007; National Osteoporosis Foundation 2010). PTH is also approved for men and women with glucocorticoid-induced osteoporosis at high fracture's risk and in men with hypogonadal osteoporosis (Canalis et al. 2007).

Despite all efforts made with PTH, the limited effect on nonvertebral fractures, the costs, the inconvenient route of administration, the activation of bone resorption, and the loss of efficacy with time suggest that PTH, although the best anabolic option today, will ultimately only partially meet the medical needs. Reducing the impact of some of these limitations constitutes the basis for current attempts to develop small molecules affecting the secretion of endogenous PTH and to use different routes of PTH administration (Roland Baron and Hesse 2012).

3.1.1 Teriparatide [PTH(1–34)]

Teriparatide has been approved for the treatment of osteoporosis at the dose of 20 µg once daily. It has been demonstrated effective in reducing the risk of vertebral and nonvertebral fractures and increasing vertebral, femoral, and total-body BMD, compared to placebo (Neer et al. 2001). In clinical trials, the safety and efficacy of teriparatide therapy has not been demonstrated beyond 2 years of treatment (Canalis et al. 2007). As a consequence, the recommended duration of teriparatide treatment in Europe is 24 months.

3.1.2 Parathyroid Hormone [PTH(1–84)]

Parathyroid hormone is approved in some countries of Europe as 100 µg-daily dose. It was found effective in reducing the risk of new or worsened vertebral fractures in postmenopausal women with osteoporosis and increasing BMD at both vertebral and femoral sites compared to placebo (Greenspan et al. 2007). As for teriparatide, in Europe the recommended duration of PTH (1–84) therapy is 24 months.

3.1.3 Safety

Adverse effects of PTH therapy include mild hypercalcemia, hypercalciuria, a possible rise in serum uric acid concentration, dizziness, nausea, vomiting, headache, and leg cramps (Neer et al. 2001; Canalis et al. 2007; Greenspan et al. 2007; Roland Baron and Hesse 2012). In clinical practice, serum calcium and 24-h urinary calcium excretion is usually checked 1 month after initiating PTH therapy. However, hypercalcemia and hypercalciuria are generally reversed by reducing calcium or

vitamin D supplementation and eventually by a dose reduction of PTH to every-other day administration.

PTH is contraindicated in patients with Paget's disease of bone, skeletal metastases, skeletal malignant conditions, history of bone irradiation, unexplained elevations in alkaline phosphatase, myeloma, hyperparathyroidism, hypercalcemia, and end-stage renal failure.

3.1.4 PTH and Antiresorptive Sequential Therapy

Some studies demonstrated a rapid and progressive decline in BMD throughout the period following PTH therapy, particularly during the first 6 months (Bilezikian 2008). Therefore, it is common practice to follow PTH treatment with an antiresorptive agent, usually a bisphosphonate, in order to both exploit its own benefits and maintain densitometric gains achieved with PTH (Canalis et al. 2007; Bilezikian 2008; National Osteoporosis Foundation 2010).

4 Strontium Ranelate

Strontium ranelate is made up of an organic anion (ranelate) and two stable strontium cations and is incorporated into the crystal structure of bone (Marie 2006). In vitro models reported anabolic and antiresorptive actions of strontium ranelate that could both reduce osteoclast-mediated resorption and increase osteoblastic differentiation (Hamdy 2009). Strontium ranelate was found to reduce incidence of new vertebral and nonvertebral fractures in postmenopausal women with osteoporosis in two randomized, placebo controlled trials of 3 years' duration (Meunier et al. 2004; Reginster et al. 2005). The reduction of hip fractures was shown only among a high risk group of patients (Reginster et al. 2005). Strontium ranelate is currently approved in Europe for treatment of postmenopausal osteoporosis at the oral dose of 2 g once daily. Adverse effects include: nausea, diarrhea, headache, dermatitis and eczema, venous-thrombosis embolism event (Meunier et al. 2004; Reginster et al. 2005). Moreover, a few cases of drug rash with eosinophilia and systemic symptoms syndrome were reported. The mechanism associated with this potentially fatal adverse effect is not understood. Anyway, therapy with strontium ranelate should be finally discontinued in case of skin rash.

5 Calcium and Vitamin D

An adequate daily calcium and vitamin D intake is a safe and inexpensive treatment to prevent osteoporosis-related bone loss and fracture and is of utmost importance for any therapeutic intervention. Indeed, calcium and vitamin D supplementation has been demonstrated as effective in reducing risk of fracture and bone loss at both hip and spine on an average of 3–5 years' treatment duration, compared to placebo (Tang et al. 2007).

Furthermore, hypovitaminosis D is a widespread condition with important health consequences such as bone loss, proximal muscle weakness, increase in body sway, falls, and fractures (Lips 2001; Holick 2007; Holick and Chen 2008). Finally, calcium and vitamin D depletion was associated with a reduced response to antiresorptive agents in terms of both BMD changes and anti-fracture efficacy (Nieves et al. 1998; Adami et al. 2009). By the way, a daily calcium intake of at least 1,000 mg/day in men and women younger than 50 years and of 1,200 mg/day for those 50 years and older is strongly recommended (National Osteoporosis Foundation 2010). Moreover, a daily intake of at least 800–1,000 IU of vitamin D is currently recommended as both food fortification and oral supplementation (National Osteoporosis Foundation 2010) and two inactive forms of vitamin D are currently available for oral supplementation: cholecalciferol and ergocalciferol. However, definite clinical recommendations concerning the optimal dose and dose intervals of vitamin D administration needed to achieve and maintain the target vitamin D serum level are still lacking. Accordingly, in clinical practice, an adequate vitamin D serum concentration could be ensured with both daily and intermittent supplementation of high dose of vitamin D. Recent data from our group showed in fact that a single large dose of vitamin D is effective in rapidly and safely enhancing serum vitamin D concentration and that cholecalciferol has a greater potency than ergocalciferol in enhancing serum vitamin D concentration (Romagnoli et al. 2008; Cipriani et al. 2010).

6 Future Directions

6.1 Cathepsin K Inhibitors

Cathepsin K is a serine protease released by activated osteoclasts into the bone resorption compartment beneath osteoclasts during bone remodeling. This protease helps degrade type 1 collagen and other proteins embedded within bone matrix during bone resorption (Costa et al. 2011). Several phase 2 trials with cathepsin K inhibitors such as odanacatib (MK-0822) (Bone et al. 2010) have been completed, demonstrating mild to moderate antiresorptive effect. However, this compound seems to stimulate bone formation on periosteal surfaces while at the same time inhibiting bone resorption on trabecular surfaces. Side effects reported with early cathepsin K inhibitors included morphea.

6.2 Modulating the Canonical Wnt-Signaling Pathway

Although activation of the Wnt signaling pathway is a very promising approach for the development of bone anabolic drugs, safety concerns exist, in particular regarding possible

oncogenic effects and uncontrolled formation of bone. However, it is important to mitigate these potential concerns with the fact that therapeutic intervention will not eliminate entirely the endogenous inhibitor and will occur only over a limited period of time.

6.2.1 Sclerostin Antibody

Sclerostin is a secreted cysteine-knot glycoprotein produced by the *SOST* gene almost exclusively in osteocytes (Baron and Rawadi 2007). Osteocytes form new bone at sites of increased mechanical strain. New bone formation caused by mechanical strain is normally stimulated by LRP 5/6 signaling through the canonical Wnt pathway (Li et al. 2005). Sclerostin normally inhibits new bone formation by inhibiting stimulatory interactions of Wnt proteins with the LRP-5/6 receptor on the plasma membrane of osteoblasts and osteoblast precursors on bone surfaces, thereby decreasing Wnt signaling through the canonical β -catenin pathway, and leading to decreased osteoblast recruitment and activation (Robling et al. 2008). LRP-5/6 signaling is normally inhibited by dickkopf/homolog 1 (Dkk1), secreted frizzled-related protein, or both.

A monoclonal antibody to sclerostin has been shown to inhibit sclerostin activity, thereby upregulating osteoblast Wnt signaling through the canonical β -catenin pathway and stimulating osteoblast recruitment and activity (van Bezooijen et al. 2005). Recently, the first human phase I randomized, double-blind, placebo-controlled clinical trial testing ascending single doses of AMG785, a humanized monoclonal sclerostin antibody, in healthy men and postmenopausal women was reported (Padhi et al. 2011). Bone formation markers increased within 1 month after a single sc dose of 10 mg/kg AMG 785 and markers of bone resorption decreased. Likewise, the gain in BMD at the lumbar spine and total hip was comparable or even greater than with rhPTH (Padhi et al. 2011). Injection site reactions were the most frequently reported adverse events. These studies point to the promising future of sclerostin antibodies for the treatment of low bone mass diseases.

6.2.2 Dkk1 Antagonists

Dkk1 is also an endogenous inhibitor of Wnt signaling. Although sclerostin antibodies are probably the preferred and most advanced therapeutic option for osteoporosis, antibodies to Dkk1 are also being developed. If proven safe and efficacious, these antibodies could also find their way to a more general indication in low bone mass diseases, although the possibility that Dkk1 is less restricted to the bone microenvironment than sclerostin may raise more concerns about off-target effects.

overall scientific guide in the choice of a drug rather than another (Reid et al. 2009), except in small trials carried out in patients taking glucocorticoids (Reid et al. 2009; Saag et al. 2009). Hence, the choice of osteoporosis therapy should be individualized for each patient, taking into consideration the efficacy, safety, cost, convenience, and other non-osteoporosis-related benefits of each potential drug in relation to the patient's needs (Qaseem et al. 2008). Treatment's discontinuation represents the great challenge for the management of osteoporosis, resulting in increased fracture risk, hospitalization, and health care costs (Kothawala et al. 2007; Siris et al. 2009). Physicians' and patients' awareness about the need to use osteoporosis medication is therefore of utmost importance as well as strategies to improve adherence to treatment. Several clinical trials for osteoporosis treatment are ongoing, testing new antiresorptives, different forms of rhPTH, or agents that activate Wnt signaling. In many of these trials, combinations and sequences of these agents with various antiresorptives are also being tested. The next few years will therefore be very exciting for osteoporosis treatment.

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7 Conclusions

Currently approved osteoporosis therapies have been demonstrated as effective in lowering fracture risk. However, at the present, we have no comparative study able to give an

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Osteoporosis and Bone Densitometry Measurements

Guglielmi, G. (Ed.)

2013, X, 198 p., Hardcover

ISBN: 978-3-642-27883-9