New Agents for the Treatment of Osteoporosis

Osteoporozda Yeni Tedavi Ajanları

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Summary

Postmenopausal osteoporosis is characterized by an increase in resorption and inadequate bone formation. Alteration in bone remodeling is associated with an accelerated risk of fracture. Pharmacological agents that increase bone mass, reduce bone loss or decrease fracture risk have become available in the last few decades. Current compounds used for the treatment of osteoporosis mostly inhibit osteoclast-mediated bone resorption, while few others have an anabolic effect. Inhibition of bone resorption by currently available agents does not restore bone structure or bone that has already been lost and it is coupled with inhibition of bone formation. The identification of new pathways involved in bone turnover, will accelerate clinical research to develop new formation-stimulating and resorption-inhibiting agents with improved safety profile and efficacy in fracture prevention in osteoporosis. In the light of new data, it is estimated that novel antiosteoporotic compounds will increase considerably in the coming years. *Turk J Phys Med Rehab 2011;57:165-71.*

Key Words: Osteoporosis, anabolic agents, antiresorptive agents, new therapies

Özet

Postmenopozal osteoporoz artmış kemik rezorpsiyonu ve yetersiz kemik formasyonu ile karakterizedir. Kemiğin yeniden düzenlenmesi (remodeling) sürecindeki bozulmalar artmış kırık riski ile ilişkilidir. Geçtiğimiz dekadlarda kemik kütlesini arttıran, kemik kaybını azaltan ve kırık riskini azaltan farmakolojik ajanlar kullanıma girmiştir. Osteoporoz tedavisinde kullanılan güncel bileşikler çoğunlukla osteoklast aracılı kemik rezorpsiyonunu inhibe etmekteyken, daha azının anabolik etkisi bulunmaktadır. Halen kullanımda olan ajanlarla kemik rezorpsiyonu inhibisyonu kemiğin yapısını düzeltememekte, kaybedilen kemiği yerine koyamamakta ve aynı zamanda kemik formasyonunda da inhibisyona yol açmaktadır. Kemik döngüsündeki yeni yolakların ortaya çıkarılması osteoporozda kırık önlenmesi ve emniyet profili açısından daha etkili kemik formasyonunu arttıran ve rezorpsiyonunu inhibe eden ajanların geliştirilmesine yönelik klinik araştırılmaların artmasına yol açacaktır. Yeni verilerin ışığında önümüzdeki yıllarda yeni antiosteoporotik bileşiklerin azımsanmayacak oranda artacağı tahmin edilmektedir. *Türk Fiz Tıp Rehab Derg 2011;57:165-71.*

Anahtar Kelimeler: Osteoporoz, anabolik ajanlar, antirezorptif ajanlar, yeni tedaviler

Introduction

Osteoporosis is defined as a systemic impairment of the skeleton characterized by low bone mass and microarchitectural deterioration of bone tissue, which increases bone fragility and susceptibility to fracture (1).

For more than two decades, osteoporosis has been accepted worldwide as a major public health problem. It is estimated that approximately 30% of women in developed countries have osteoporosis with at least 40% of these women predicted to have at least one fragility fracture in their remaining lifetime (2). Hip and vertebral fractures are associated with an increased rate of morbidity and mortality (3).

Medical, social, psychological and economic burden caused by osteoporosis will increase linearly as the population ages. Therefore, the treatment of osteoporosis will be an important medical challenge for all societies. The first step of therapy in osteoporosis is to prevent the first fracture and if occurred, reduce the risk of eventual new fractures. In the past decades, effective pharmacological agents capable to improve bone mineral density

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(BMD) and decrease the incidence of fractures, including both vertebral and non-vertebral fractures, were developed and widely used. The introduction of potent agents capable of inhibiting bone resorption, such as bisphosphonates and selective estrogen receptor antagonists, have made a major impact on the treatment of osteoporosis. The current antiresorptive agents have been shown to significantly reduce the incidence of fractures, including both vertebral and non-vertebral fractures, particularly hip fractures. Most current agents are antiresorptive and eventually lead to a decrease in osteoblast function. These antiresorptive agents include bisphosphonates, calcitonin and selective estrogen receptor modulators, with adequate calcium and vitamin D supplementation. In more limited indications, anabolic agents such as parathyroid hormone (PTH) can be an alternative therapy agent. Strontium ranelate both acts as a bone formation stimulator and an antiresorptive agent (4-10).

It has been shown that most of the antiresorptive drugs do not restore bone structure or bone that has already been lost. Bisphosphonates have now been in use for more than 10 years and there is some concern that long-term use may cause excessive inhibition of bone remodeling and increase in microcracks. In recent years, osteonecrosis of the jaw has also been increasingly suspected to be a potential complication of notably injectable bisphosphonate therapy (11).

Exploration of different pathways and regulatory mechanism in bone remodeling, will result in the development of novel therapies. Therefore, reduction of the risk of fracture and side effects above the level of conventional drugs are principal requirements for any novel osteoporotic drug to be registered.

Bone Biology

Bone is continuously remodeled throughout life, due to a very active turnover process in different pathways, acting enzymes and cytokines functioning with proper coordination. The remodeling process is mandatory for bone to preserve its normal integrity, quality and strength (12). Bone remodeling takes place at bone remodeling units (BRU). The resorption process starts with the stimulation of osteoclast development when bone tissue presents microcracks and deformation. Over duration of 3 weeks, osteoclasts create resorption cavities after resorbing the old bone. Bone resorption is followed by activation of osteoblasts and formation of osteoid. During this latter period of formation of about 3 months, resorption cavities are filled (13).

At the end of this complex cycle, the amount of new bone equals the amount of resorbed bone. Osteblasts and osteoclasts are not the only cellular elements contributing to the bone turnover process. When active matrix synthesis is over, osteblasts become embedded in the matrix and are transformed as osteocytes. Osteocytes which are derived from osteoblasts make up over 90% of the cells in bone. They act as carriers of signals on bone surface both to osteoblasts and osteoclasts (14). Osteocytes also maintain connections to other osteocytes, the BRU and the bone surface by means of a wide canalicular network. This network acts as a passage of fluid which conveys signals. Osteocytes are involved in both phosphate and calcium metabolism and can remodel perilacunar matrix (15,16).

Bone remodeling is an active and dynamic process which is maintained in a continuous equilibrium. In humans, the skeleton terminates its complete turnover every 10 years. On the other hand, during postmenopausal period, estrogen deficiency results with increased bone turnover with an excess of resorption over formation. This consecutive formation and resorption cycle enables the use of pharmacological agents that act either by reducing resorption (antiresorptive therapy) or by augmenting formation (anabolic therapy) (17).

1. New Antiresoptive Agents

There is a tight relation between bone resorption and formation with most of currently available antiresorptive agents; inhibition of resorption eventually results in inhibition of formation. Theoretically, an agent that inhibits bone resorption but allows bone formation to continue would, therefore, have a greater effect on bone quality and bone mass than the currently used antiresorptive compounds.

1.1 Glucagon-Like Peptide 2

Glucagon-like peptide 2 (GLP-2) is an intestinal hormone released in response to food intake. Eating reduces bone remodeling through release of GLP-2, whereas nocturnal fasting enhances bone remodeling. Bone remodeling occurs according to a circadian rhythm, with a nocturnal rise in bone resorption (18,19). In other words, the rhythm is affected by rates of food intake and increases overnight with nocturnal fasting. Treatment with GLP-2 at bedtime results in a substantial reduction in the bone resorption that normally occurs overnight. GLP-2 does not appear to reduce bone formation, as evidenced by stable osteocalcin levels during treatment (20). A 4-month, phase-2 trial in 160 postmenopausal women given GLP-2 resulted in an increase in hip bone density and a reduction in the nocturnal rise in C-telopeptide concentrations, a marker of bone resorption, with no effect on osteocalcin, a marker of bone formation (21,22).

Inhibition of resorption with available antiresoptive agents also results in inhibition of formation. An agent that inhibits the resorption but allows formation to continue would be the best choice for osteoporosis treatment. If this pattern could be sustained, GLP-2 would have an advantage over available antiresorptive agents that decrease bone formation (22).

1.2 Cathepsin K Inhibitors

Cathepsin K is a lysosomal cysteine protease that is selectively expressed by osteoclasts and contributes to the breakdown of the bone matrix. Cathepsin K is expressed not only by osteoclasts, but also by the heart, lungs and liver (23). Elimination of cathepsin K in osteoclasts results in inhibition of bone resorption. Inhibitors of cathepsin K are suggested to have less effect on osteoclast-osteoblast interaction, resulting in less inhibition of bone formation, than the available antiresorptive agents (22,24).

Two cathepsin K inhibitors, balicatib and odanacatib, have been tested in humans and shown to reduce markers of bone resorption and increase bone mass (24-26). The multicenter, randomised, placebo-controlled trial with balicatib was a dose-range finding study done in 675 postmenopausal women. Markers of bone resorption declined more than 55% with no decline in markers of bone formation and increase in BMD. Skin reactions, including pruritus, scleroderma-like lesions and morphea-like changes were noted in a small number of patients (27).

As a result of side effects, especially skin reactions, drug development of all catepsin K inhibitors has been suspended,

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except for odanacatib. Balicatib inhibited not only cathepsin K, but also cathepsins B and L. Odanacatib is more specific for cathepsin K, which may explain the less frequent side effects and also has stronger resorption inhibiting effects (22,24,25). The 2-year results of a randomised, controlled trial of 399 postmenopausal women have been reported. Odanacatib was given 3 mg to 50 mg as a weekly oral dose and dose-dependent increase was shown in spine and hip density together with decline in bone resorption markers. With 50 mg/week, the increases were 5.5% at the spine and 3.2% at the femoral neck. BMD at these sites was essentially unchanged with placebo. Serum C-terminal telopeptides of type-I collagen (CTx) was 40% and urine N-terminal telopeptide of type-I collagen (NTx) was 52% lower in the patients treated with 50 mg/week odanacatib. Decline in bone formation markers was much smaller. Serum bone-specific alkaline phosphatase was found to be 13% lower in the treatment group. These findings suggested less inhibition of bone formation than found with current antiresorptive therapies (28,29). Adverse reactions with odanacatib were close to those with placebo and scleroderma-like cutaneous lesions were not seen. Odanacatib was found to be safe and well-tolerated with no difference in side effects with high doses, including skin reactions and rash (26,29). A one-year extension study further assessed odanacatib efficacy and safety (30). Two years later, the patients were randomized again to 50 mg/week odanacatib or placebo. Continued treatment with 50 mg of odanacatib for 3 years showed significant increase from baseline. BMD increase at the spine and hip was 7.9% and 5.8%, respectively. Urine NTx remained suppressed at the end of the third year. Bone specific alkaline phosphatase was relatively unchanged compared with the baseline. Treatment cessation resulted in bone loss in all sites, but BMD remained at or above baseline. There were similar adverse event rates in treatment and placebo groups and treatment was well-tolerated. It is reported that 3 years of odanacatib treatment resulted in progressive increase in BMD, but the effect was reversible (30).

1.3 Denosumab

Receptor activator of nuclear factor kappaB ligand (RANKL) is the principal mediator of bone remodeling by regulating osteoclastic bone resorption. RANKL, a member of the tumor necrosis factor (TNF) receptor family, is produced by osteoblasts and expressed on their surface. RANKL binds to and interacts with receptor activator of nuclear factor kappaB (RANK) on the surface of osteoclasts to stimulate their activation and differentiation leading to increased bone resorption (31,32).

Osteoprotegerin (OPG), another member of the TNF receptor family, is a soluble decoy RANKL receptor and binds to RANKL. OGP acts as RANKL antagonist, thus resulting in the prevention of RANKL to interact with RANK. This event leads to less osteoclast activation and decrease the survival of existing osteoclasts (33). Various conditions including menopause, in which decline of the level of sex hormones is present, are associated with an activated RANKL/RANK pathway and increased bone resorption (34). The key role of RANKL in the pathogenesis of postmenopausal osteoporosis has prompted the development therapeutic agents which can down-regulate RANKL. The RANKL inhibitor that is being developed is the human anti-RANKL antibody denosumab (AMG 162). Denosumab is a high affinity fully human monoclonal IgG2 antibody that binds selectively to RANKL. It mimics the effect of OPG on RANKL with a superior

pharmacokinetic properties compared with OPG (18). Denosumab has a long duration of activity. Following 60 mg subcutaneous injection of denosumab every 6 months, the median time to maximum concentration after the first dose is 26 days. Long half-life and a high antiresorptive property at early stages of osteoclast differentiation are thought to be the causes of its extented activity (35).

Characteristics, such as mechanism of action and effects on bone parameter, of denosumab reveal some significant differences from bisphosphonates. The levels of bone turnover markers decrease more rapidly) following denosumab injection when compared to bisphosphonates within few days. A similar process is also observed after discontinuation, thus, bone markers recover to normal levels more rapidly than with oral bisphosphonates. Unlike bisphosphonates, denosumab has reversible effects because it is not incorporated into the bone mineral and does not accumulate in the bone. Gastrointestinal side effects are uncommon. Biannual subcutaneous administration could improve long-term adherence to therapy. Since denosumab is not eliminated from the kidney, it can be considered as treatment option for patients with impaired renal function (36,37).

In a phase-2 study, efficacy and safety of denosumab has been evaluated comparatively to placebo and to alendronate. In 412 postmenopausal women with low BMD, denosumab was given in a dosage of 6 to 30 mg every 3 months or 14 to 210 mg every 6 months; the alendronate dosage was 70 mg/week. The primary endpoint was the percentage change in lumbar spine BMD at 12 months compared to baseline versus placebo. Data at 12, 24 and 48 months were reported (38). After 12 months of denosumab administration, a dose-dependent significant increase of 3.0–6.7% in lumbar spine BMD was observed (39). At 24 months, lumbar spine BMD increase was found ranging from 4.1% to 8.9%. These findings supported and extended the data obtained at 12 months. BMD gains at the hip and forearm were greater with denosumab than with alendronate. Adverse events were similar in the placebo, denosumab, and alendronate groups. No patient developed neutralizing antibodies during 24 months of the trial. Although six cases (1.9%) of serious adverse events consisting different infections in the denosumab group (two cases of diverticulitis, three cases of pneumonia, and one case of labyrinthitis) compared to none in the placebo group or alendronate group were reported (40). The extension of the study for 24 months beyond the initial 24 months, with denosumab-treated patients, revealed that continuous denosumab treatment for 48 months increased BMD at the lumbar spine (9.4–11.8% compared to baseline) and total hip (4.0–6.1% compared to baseline), with consistent suppression of bone turnover markers during the study. Discontinuation of denosumab after 24 months of treatment was associated with a BMD decrease of 6.6% at the lumbar spine and 5.3% at the total hip within 12 months of discontinuation. When denosumab was readmistered, BMD values increased to an extent similar to what was observed with initial treatment (9.0% and 3.9% increase at lumbar spine and total hip, respectively, compared with original baseline values. The overall incidence of malignant neoplasms and infection showed no significant difference among the treatment groups (38).

FREEDOM study is a phase-3 multicenter randomized placebo-controlled study of denosumab in 7868 patients with postmenopausal osteoporosis (mean age, 72 years). The effects of

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denosumab on vertebral and non-vertebral fractures in a dosage of 60 mg every 6 months for 3 years were investigated. Compared to placebo, denosumab group had 68% fewer new vertebral fractures, 20% fewer non-vertebral fractures overall, and 40% fewer hip fractures and BMD increases of 9.2% at the spine and 6% at the total hip. In the denosumab group, there was a 72% decrease in serum CTx. Denosumab was well-tolerated. There was no increase in the risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia, and there were no cases of osteonecrosis of the jaw and no adverse reactions to the injection of denosumab (41).

Another phase-3 placebo-controlled trial, DEFEND (DEenosumab FortifiEs boNne Density), investigated the percentage change from baseline to 24 months in lumbar spine BMD measured by DXA in 332 postmenopausal women with lumbar spine T-scores between -1.0 and -2.5 compared to placebo (42). Significant increase in BMD at the lumbar spine with denosumab compared with placebo at 24 months (denosumab 6.5% vs. placebo 0.6%) was found. On other investigated sites (total hip, one-third radius, and total body), significant increase in volumetric BMD were also reported. Denosumab administration revealed a significant decrease in CTx-I, TRAP-5b, and P1NP compared with placebo.

DECIDE (Determining Efficacy: Comparison of Initiating Denosumab vs. alEndronate), a 1-year phase-3 study in 1189 postmenopausal women with postmenopausal osteoporosis, compared 60 mg of denosumab subcutaneously administered every 6 months to 70 mg/week alendronate. The primary endpoint was percentage change from baseline in the total hip BMD values. Other outcome measures were the effects on bone remodeling markers, serum CTx and P1NP. At 12 months, there was a significantly greater BMD increase with denosumab compared with alendronate at the total hip (denosumab 3.5% vs. alendronate 2.6%). On all measurement sites also, the BMD increase was larger with denosumab than with alendronate. There was greater suppression of BTMs with denosumab after 1 and 6 months. The adverse event rates were similar between the two groups (43).

In 1-year phase-3 double-blind, controlled trial, STAND (Study of Transitioning from AleNdronate to Denosumab), the effects of denosumab in 504 postmenopausal women aged 55 and older previously treated with alendronate, were assessed. The primary endpoint was percentage change in BMD at the total hip at 12 months for denosumab compared to alendronate. Denosumab group demonstrated a statistically significant greater increase in BMD compared with alendronate at the total hip, lumbar spine, and distal one-third radius. Data suggested that denosumab, given after alendronate in postmenopausal women, increased BMD more than in those continuing alendronate, with a similar incidence of adverse events (44).

Randomized controlled trials indicate that denosumab is an effective resorption inhibitor alternative to bisphosphonates both for the first-line treatment of osteoporosis and after bisphosphonate therapy. Although in "FREEDOM" trial the efficacy of denosumab in the reduction of fracture rate versus a placebo was demonstrated, there are yet no studies that have compared fracture rates with denosumab and bisphosphonates.

Denosumab has recently been approved in the USA for osteoporosis and bone metastases and in Europe for osteoporosis.

1.4. αvβ3 Antagonists

Integrins are transmembrane adhesion receptors mediating cellular interactions. αvβ3 integrin is a relatively specific and the most abundant integrin in the osteoclast which plays a critical role in both migration and adhesion of osteoclasts on bone surfaces (25). An oral, non-peptide integrin antagonist was tested in a multicenter, randomized, double-blind, placebo-controlled study involving women with low lumbar spine or femoral neck BMD. In this study, lumbar spine BMD significantly increased and markers of both bone resorption and formation decreased (45).

1.5. Src Tyrosine Kinase Inhibitors

Similar to αvβ3, Src is involved in osteoclast-mediated bone resorption. Osteoclasts from the src null mice formed increased number of osteoclasts but failed to resorb bone because they could not form ruffled borders (46). The effect of an orally available Src inhibitor saracatinib was assessed in healthy men which led to dose-dependent decrease in bone resorption markers without a significant effect on formation markers (47). Saracatinib is currently being explored in phase-2 studies for osteosarcoma and bone metastasis but not for osteoporosis (18).

1.6. Vacuolar H+-ATPase Inhibitors

Osteoclastic bone resorption occurs via the vacuolar H+-ATPase which pumps protons out into the lacuna. Bafilomycin which is not selective for any particular type of vacuolar H+-ATPase inhibited bone resorption in osteoclast cultures (48). Later, a relatively osteoclast-selective H+-ATPase inhibitor was shown to inhibit ovariectomy-induced bone loss in rats (49).

2. New Anabolic Agents

Anabolic agents have the potency to augment bone mass and strength, improve bone quality to a greater degree than antiresorptive agents.

2.1. Wnt Signaling Inhibitors

After the advent of PTH as an effective anabolic therapy, other potential targets aiming to restore bone mass became a focus of interest. Among these, Wnt/β-catenin has been recognized as a result of genetic studies in mouse and human subjects. Wnt proteins regulate cell-cell interactions during embryogenesis, cancer and bone homeostasis (50). The first link between Wnt signaling and human bone disease came from the observations that inactivating mutations in the Wnt coreceptor, LRP5, cause the osteoporosis-pseudoglioma syndrome (51). At the molecular level, activation of the canonical Wnt/ β-catenin pathway is the master switch for osteoblastic differentiation (52).

Wnt proteins bind to a receptor complex of lipoprotein receptors (LRP) 4,5 and 6 and frizzled proteins which activates a protein complex (axin, adenomatous polyposis coli and glycogen synthase kinase 3β) leading to accumulation of β-catenin. β-catenin accumulation affects gene transcription which is important in bone formation (22, 50).

Wnt/β-catenin pathway offers many extracellular and extracellular potential binding sites that can be used as a target for pharmacological intervention. These sites include: secreted frizzled-related proteins (SFRPs), sclerostin, dickkopt (DKK) proteins and the intracellular glycogen synthase kinase-3β. Since the activation of the pathway leads to increased bone formation, aim of therapeutic interventions is to increase the Wnt/β-catenin canonical signaling.

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2.1.1. Inhibition of Frizzled-Related Proteins (SFRPs)

SFRP1 antagonizes canonical Wnt signaling either by interacting with Wnts to prevent them from associating with Fzd receptors or by binding directly to frizzled proteins to form a nonfunctional complex (53). Ablation of SFRP-1 gene (SFRP -/-) in mice increased trabecular BMD, volume, and mineral apposition rate in multiple skeletal sites when compared with +/+ controls besides inhibition of osteoblast apoptosis while enhancing proliferation and differentiation of these cells (54). Several potential SFRP1 antagonists are identified, however, their effect on in vivo parameters has yet to be reported (55).

2.1.2 Inhibition of Sclerostin

Sclerostin, the protein product of SOST, is a circulating inhibitor of the Wnt-signaling pathway that achieves this by binding to LRP5 and LRP6 (56). In the genetic diseases van Buchem's disease and sclerosteosis, a link between this osteocyte-secreted protein and bone mass has been observed. In the ovariectomized rat model, sclerostin antibody treatment led to marked increases in bone formation on trabecular, periosteal, endocortical, and intracortical surfaces (57). As well as ovariectomized rat model, Lin et al. (58) investigated the effect of sclerostin in disuse osteoporosis using mutant mice and concluded that Sost (-/-) mutant mice were resistant to mechanical unloading-induced bone loss. This finding elucidated the mechanism underlying the response of bone to mechanical unloading is mediated through sclerostin, thus Wnt/β-catenin pathway, since sclerostin is produced solely in osteocytes. In primates, sclerostin-neutralizing monoclonal antibody administered to gonad-intact female monkeys had clear anabolic effects and significantly increased bone mineral content and density at several skeletal sites including femoral neck, radial and tibial metaphyses (59). The first-in-human study was conducted by Padhi at al. on 72 healthy subjects (both men and postmenopausal women) (60). In this study, AMG 785 (antibody for sclerostin) was administered subcutaneously or intravenously in various doses and followed for 85 days. AMG 785 was generally well-tolerated (one case of nonspecific hepatitis and 6 cases developed anti-AMG 785 antibodies) and anabolic effects were established. AMG 785 is now being investigated in a trial on postmenopausal women with low BMD (versus alendronate and teriparatide) which is expected to be completed in 2012 (18).

2.1.3. Inhibition of Dickkopt 1 (DKK-1) Action

DKK1 is a high-affinity antagonistic ligand for LRP6, which is a Wnt coreceptor that acts together with the frizzled serpentine receptor to initiate Wnt signal transduction (61). Diarra and colleagues (62) were able to reverse the bone-destructive pattern of a mouse model of rheumatoid arthritis to the bone-forming pattern of osteoarthritis by inhibiting DKK1. In this study, inhibition of Wnt led to formation of osteophytes, bony spurs and joint fusions resembling anabolic forms of human arthritis. In the mouse model, it was demonstrated that DKK1 is a key player in multiple myeloma and that blocking DKK1 activity in myelomatous bones reduces osteolytic bone resorption, increases bone formation, and helps control multiple myeloma growth (63). This findings were reproduced in further studies (64,65). DKK1 inhibition is currently being investigated in patients with refractory multiple myeloma and the research is expected to be completed in 2012 (18). DKK1 have not yet been investigated in osteoporosis.

2.1.4. Inhibition of GSK-3β

Inhibition of Wnt/β catenin pathway at a later step is possible through inhibition of GSK-3β which would lead to stabilization of β-catenin instead of degradation, thus activating Wnt pathway. Rodent studies are promising, however, this enzyme participates in many cell functions, so skeletal anabolic use might require application of targeted therapy (25).

2.1.5. Potential Risks of Wnt/β Catenin Pathway Inhibition

Wnt pathway has various functions in cells other than bone which needs to be considered. Wnt signaling has been associated with human malignancies such as colorectal and hepatocellular cancer (66). Aberrations in Wnt signaling can lead to gastrointestinal disorders such as adenomatous polyposis, predisposing patients to colorectal cancers (67). In addition to gastrointestinal cancers, concerns regarding increased risk of osteosarcoma were suggested through analysis of 5 human osteosarcoma cell lines (68). Due to these findings, tissue-specific targeting of these new anabolic therapies seems to be crucial for long-term safety.

2.2 Calcilytic Agents

Calcilytic drugs act as antagonists of calcium-sensing receptors leading to hypocalcemia, thus stimulating pulsatile release of PTH from parathyroid cells. The aim is to develop a drug that has a very short half-life and achieves a rapid and transient peak of PTH release, in order to reproduce the in vivo anabolic action of intermittent pulses of PTH (25). In an ovariectomized rat model of bone loss, daily oral administration of calcium-sensing receptor antagonist promoted bone formation and improved parameters of bone strength at lumbar spine, proximal tibia and midshaft femur (69). In this study, in healthy volunteers, single doses of intravenous and oral forms elicited transient elevations of endogenous PTH concentrations in a profile similar to that observed with subcutaneous PTH. The most advanced compound of this class, MK-5442, is currently in phase-2 trials for postmenopausal osteoporosis (18).

Conclusion

Presently available antiresorptive treatments are effective in reduction of osteoporotic fragility fractures, but some are limited by side effects, insufficient long-term compliance, concurrent comorbidities. Antiresorptive drugs, in particular aminobisphosphonates, can suppress in a great extent bone turnover, which might contribute to the pathogenesis of serious side effects such as osteonecrosis of the jaw. Some of the new antiresorptive agents acting via distinct cellular mechanisms seem to not affect normal osteoblastic bone formation, consistent with an uncoupling effect while suppressing bone. Whether these uncoupling compounds have an advantage over conventional antiresorptives remains to be seen. In more severe osteoporosis with excessive bone loss, multiple fractures and impaired fracture healing, there is a great need for additional therapy modalities. Wnt signaling inhibitors and calcilytic drugs are promising new anabolic agents

It is obvious that exploration of different pathways and regulatory mechanism of bone remodeling will result in the development of novel therapies. Agents that target specific peptides having key roles in osteoblast formation or osteoclast function, leading up to several promising candidates, will be potential future compounds to become effective antiresorptive or anabolic agents to treat osteoporosis.

Reduction of the risk of fracture and side effects above the level of conventional drugs, convenient mode of administration, and higher compliance are principal requirements for any new osteoporotic drug to be registered. In fact, many of the new

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drugs, both approved and still under investigation, combine efficacy with easy administration that might translate into better adherence. In the long term, efforts will be concentrated on increasing our knowledge of bone genetics and introducing patient-specific pharmacological treatments.

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