Drugs for the management of osteoporosis: a review

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ABSTRACT

Osteoporosis is characterized by low bone mass with micro architectural deterioration of bone tissue leading to enhance bone fragility, thus increasing the susceptibility to fracture. Osteoporosis is an important public health problem leading to an increased risk of developing spontaneous and traumatic fractures. In India osteoporotic fractures occur more commonly in both sexes, and may occur at a younger age than in the western countries. Although exact numbers are not available, based on available data and clinical experience, 36 million Indians may be affected by osteoporosis by 2013. This would be associated with enormous costs and considerable consumption of health resources. Pharmacological therapies that effectively reduce the number of fractures by improving bone mass are now available widely in markets. At present most drugs available in the markets decrease bone loss by inhibiting bone resorption, but the upcoming therapies may increase bone mass by directly increasing bone mass as is the case of parathyroid hormone. Current treatment alternatives include bisphosphonates, calcitonin, selective estrogen receptor modulators and inhibitors of RANK pathway but sufficient calcium and vitamin D are a prerequisite. Newer osteoclast targeted agents like cathepsin K and c-src kinase are under clinical development. The therapies which target osteoblasts include the agents acting through the Wnt-β catenin signaling pathway like Dkk-1 inhibitors and sclerostin antagonists. To further improve pharmacological interventions and therapeutical choices in this field, improvement of knowledge is very necessary.

Keywords: osteoporosis, osteoblast, antiresorptive agents, postmenopausal, bisphosphonates.

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INTRODUCTION

Osteoporosis is a multifactorial progressive skeletal disorder characterized by reduced bone mass and deterioration of bone microarchitecture, predisposing it to increased fracture risk.[1] The capacity of bone to resist mechanical forces and fractures depends not only on the quantity of bone tissue but also on its quality.[2] Osteoporosis is called a "silent disease" because it progresses without symptoms until a fracture occurs. Because of larger skeletons and no period of rapid hormonal change osteoporosis progresses more slowly in men than in women.[3] The fractures caused by osteoporosis have a great impact on public health, as they are often associated to increased morbidity, mortality and high economic cost. Thus, in the last two decades pharmacological and non-pharmacological treatment (usually based on physical exercise) options have been largely developed to reduce the risk of fractures in osteoporotic patients.[1]

At present there are many therapies available for the treatment of osteoporosis, but the existing therapies have certain issues including efficacy and long term safety issues. Estrogen role for the maintenance of bone integrity was recognized early on, but estrogen therapy has several non-skeletal adverse consequences including vascular events and breast carcinoma.[4] Hormone replacement therapy was recommended to prevent osteoporosis. However, widespread use of parathyroid hormone (PTH) is limited because of its cost, the need for daily injections and prolonged use.[5] Selective estrogen receptor modulators (SERMs) have many potential uses, and

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are currently approved for postmenopausal women with or at risk for osteoporosis. The safety profile of these agents is thus of great interest. Both tamoxifen and raloxifene are associated with a two to three fold increase in venous thromboembolic events. Lesser adverse events that are causally related to these drugs include leg cramps and an increase in reports of hot flashes.[6] Problems with side effects and in demonstrating efficacy to reduce fractures have prevented other SERMs, such as arzoxifene, from continuing toward approval.[7] From longtime osteoporosis therapeutics have been dominated by anti-resorptive agents like bisphosphonates but their anti-fracture efficacy is found to be very less than desired. According to the evidences available it is found that they can reduce fracture risk by only 50%.[8] Also, all of these anti-resorptive agents have to be given on a long term basis. Hence there are issues of safety and compliance. Osteonecrosis of the jaw (ONJ) is an uncommon adverse reaction seen with high dose intravenous bisphosphonate therapy.[9] Consequently, there is a definite need to improve upon the existing therapies and to develop newer agents which will be useful in the prevention as well as treatment of osteoporosis in the future. The aim of this paper is to describe the current status of osteoporosis in India, osteoporosis pathology, the most used therapies for osteoporosis and their clinical implications, the newer agents under clinical development and emerging therapies for the treatment of osteoporosis.

Osteoporosis in India

The population of India is expected to increase to 1,367 million by 2020 and 1,613 million by 2050; of which 9.8% (134 million) and 19.6% (315 million), respectively, will be adults over 60 years.[10] These staggering numbers give some idea of the population at risk for osteoporosis in India in the years to come. Osteoporosis is becoming a serious problem for the public economy and health, because of the increase in elderly population in the near future. Conservative estimates in a study suggest that 20% of women and about 10-15% of men are osteoporotic in India.[11] Another highly conservative estimate by a group of experts suggested that 26 million Indians suffer from osteoporosis, and this number is expected to reach 36 million by 2013.[12]

In developing countries like India hip fractures are a major health problem. Hip fractures cause mainly physical impairment and mortality in the elderly patients.[13] A survey carried out by the Indian Society for Bone and Mineral Research (ISBMR) among orthopedic surgeons across the country, revealed that in government hospitals about 80%-85% hip fractures are surgically treated whereas in private hospitals almost 100% receive surgical treatment. In government hospitals the direct cost for surgical treatment to the patient is approximately 150 USD (the cost for the prosthesis), whereas in private hospitals the direct cost for surgical treatment is about 2,500-3,000 USD.[12]

Nutritional factors

Despite abundant sunshine, vitamin D deficiency is widespread in India. A recent International Osteoporosis Foundation (IOF) report on the global status of Vitamin D nutrition highlights South Asia, especially India, as one of the most deficient regions. This is due to factors such as skin pigmentation, clothing habits and absence of vitamin D fortification.[14] Also in India calcium intakes are also far below western recommendations.[15] Thus, low vitamin D level and low calcium intake seem to be major contributing factors to poor bone health and osteoporosis in India. Differently, in other developed countries (USA and Canada), the Institute of Medicine (IOM) of the United States has recently reviewed the vitamin D and calcium intake recommendation. In this report it is recognized that the majority of American and Canadian citizens get enough vitamin D and calcium.[16] Confusion about the amount of vitamin D necessary to avoid deficiency has arisen in recent years, as tests that measure levels in patient's blood have become widely used. Poor sunlight exposure, skin pigmentation and vitamin D-deficient diet are some obvious causes for this finding. Atmospheric pollution has also been suggested as a contributor to vitamin D deficiency in both urban and semi-urban Indians, postmenopausal women, pregnant women, specifically school children and newborns.

Diagnosis

For diagnosing osteoporosis, dual energy X-ray absorptiometry (DXA) became available in India only in 1997, subsequently several other hospitals/institutions acquired DXA in the past couple of years.[11] Quantitative ultrasound (QUS) measurement of the calcaneus (heel) for determination of bone density is in use since 1984. Radiogrammetry is the geometric measurement of bone dimensions on high resolution radiographs. A study available in the abstract form has reported normative reference database for Indian men and women using digital X-ray radiogrammetry (DXR) in a cohort of 262 women and 172 men.[17] Biochemical markers of bone turnover are not yet freely available in Indian markets.[18]

Pathophysiology of bone loss

Bone resorption takes place through the action of osteoclast cells, which resorbs the bone matrix by secreting hydrochloric acid, which dissolves calcium phosphate, and enzymes such as collagenase and other proteases.

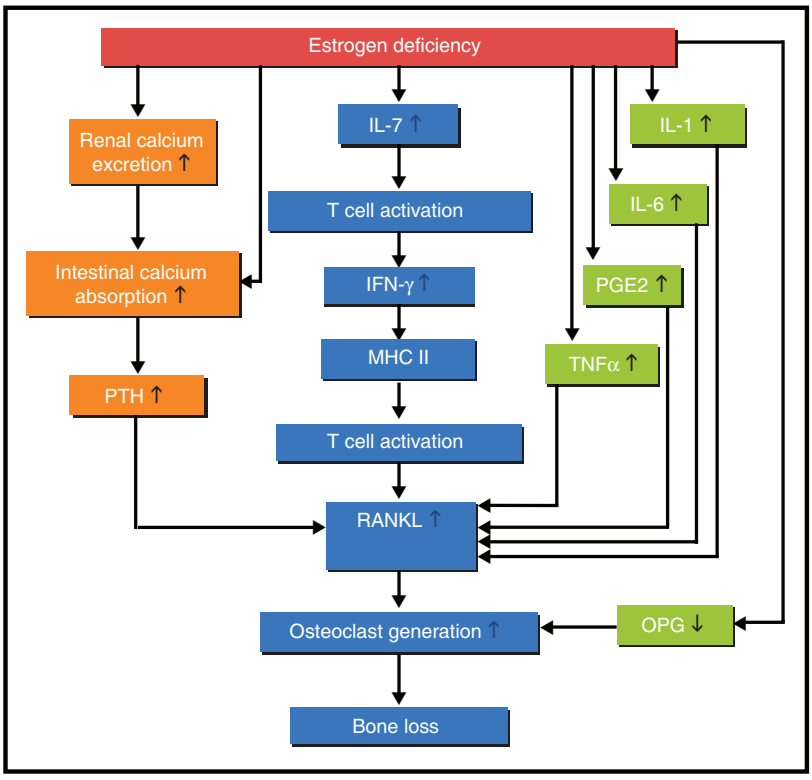

Figure 1
A model of the effects of estrogen deficiency on bone loss. PGE2: Prostaglandin E2, OPG: Osteoprotegerin, MHC II: Major histocompatibility complex class II molecules; RANKL: Receptor activator of nuclear factor-Kb Ligand; TNFα: Tumor necrosis factor; IFN-γ: Interferon; IL: Interleukin; PTH: Parathyroid hormone.

After the action of osteoclast cells at the bone resorption site, osteoblast cells synthesize new bone.[19,20] The organic component of the bone matrix, which is mainly composed of Type-I collagen fibers, is produced by Osteoblast cells. Osteonectin, sialoproteins and osteocalcin are the three important proteins secreted by osteoblast cells that are incorporated into the bone matrix. Two stages of mineralization mediated by osteoblasts then follow, firstly between the collagen fibrils hydroxyapatite crystals get deposited. In this process of mineralization alkaline phosphatase located on the membrane of osteoblast plays very important role. In the second stage deposition of additional minerals occurs on the bone resorption site.[19,23-25]

Estrogen is another systemic hormone with direct effects on bone and playing an important role in osteoporosis. In postmenopausal women, deficiency of estrogen leads to an up regulation of RANKL on bone marrow cells, which is an important determinant of increased bone resorption,[26] whereas estrogen itself stimulates OPG production in osteoblasts and thus exerts anti-resorptive effects on bone.[27]

Extra skeletal effects of estrogen deficiency are mainly based upon increased renal calcium excretion and decreased intestinal calcium absorption.[28-30] Estrogen deficiency also cause a continuous increase in serum parathyroid hormone (PTH) levels.[31-32]

The production of many different cytokines and other inflammatory mediators, such as interleukin (IL)-1, IL-6, TNF-α, and prostaglandin E_2, are involved in the pathogenesis of osteoporosis. Nevertheless, it is also known that estrogen treatment increases the production of insulin-like growth factor-1 (IGF-1) and transforming growth factor (TGF)-β by osteoblastic cells.[33,34] More recent studies deal with the effects of estrogen deficiency on T cell function. It was demonstrated that estrogen withdrawal results in increased production of IL-7, leading to T cell activation accompanied by an increased production of interferon (IFN)-γ and TNF-α by T cells.[35,36] One major action of IFN-γ is the up regulation of major histocompatibility complex (MHC) class II molecules on antigen presenting cells. This leads to a further activation of T cells, which now produce more

RANKL and TNF-α. As already mentioned, these two cytokines have a pronounced osteoclastogenic activity. The effects of IFN-γ on bone metabolism are scientifically challenging, as IFN-γ acts as pro-osteoclastogenic cytokine in the context of ovariectomy,[37] whereas it is regarded as antiosteoclastogenic in general (Figure 1).[38]

Current therapies for osteoporosis and their clinical implications

Calcium and vitamin D

As a combination therapy, calcium and vitamin D is the accepted baseline treatment for osteoporosis. In a three year clinical study, supplementation with calcium and vitamin D_3 reduced the risk of hip fractures and other non-vertebral fractures among elderly women and also a significant benefit was seen after 18 months.[39] For elderly patients treatment with Vitamin D may have additional benefits, because vitamin D therapy increases muscle strength and thus may reduce the possibility of fractures. [40,41]

The problem of calcium deficiency in senile osteoporotic patients can be corrected by administration of Vitamin D, which facilitates calcium absorption, but such treatment alone may increase risk of hypercalcemia and hypercalciuria. It has been reported earlier in many studies that bisphosphonates may cause hypocalcemia. Different mechanisms of Vitamin D and bisphosphonates suggest that a combination therapy of these agents may be very effective in improving calcium homeostasis and bone mass in patients with osteoporosis.[42]

Bisphosphonates

The most commonly prescribed drugs are bisphosphonates which are used to treat osteoporosis in the US and many other countries including India. Alendronate, a once daily oral medication, was the first bisphosphonate to be approved for treatment of osteoporosis in the US in 1995. Since that time, newer bisphosphonates with less frequent dosing intervals have been introduced, partially in an attempt to improve compliance. Risedronate is an oral medication that can be administered daily, weekly, or monthly at varying doses. Zoledronic acid is the newer medication which is administered once yearly by intravenous transfusion.[43]

Bisphosphonates bind to hydroxyapatite crystals and thus have a very high affinity for bone. Bisphosphonates are released from the bone matrix upon exposure to acid and enzymes secreted by an active osteoclast.[44,45] Out of all bisphosphonates, zoledronic acid has the highest affinity for binding to the bone mineral matrix followed by pamidronate > alendronate > ibandronate > risedronate > etidronate > clodronate.[44] Bisphosphonates with higher affinity like zoledronic acid bind avidly to the bone surface, but spread through bone slowly whereas lower affinity agents like clodronate distribute more widely through the bone, but they have shorter time of residence when the treatment is stopped. Suppression of bone resorption occurs within approximately three months of initiation of oral bisphosphonate therapy regardless of dosing frequency, but it is more rapid after intravenous administration. After three years of treatment, bisphosphonates have shown to increase BMD of the hip by 3%-6% and at the spine by 5%-8%. In women with osteoporosis zoledronic acid, alendronate and risedronate also reduced nonvertebral fractures by 25%-40%, including hip fractures by 40%-60%.[45]

Some important adverse events associated with bisphosphonates therapy

Orally administered bisphosphonates may cause irritation in the esophagus. It is recommended to swallow oral bisphosphonates with full glass of plain water on arising in the morning, remaining upright for at least 30 minutes after swallowing the tablet and discontinuing the drug promptly if esophageal symptoms develop. Rapid intravenous administration of parenteral bisphosphonates may cause renal toxicity. For patients with creatinine clearance less than 30-35 mL/min, use of parenteral bisphosphonates is not recommended.[46]

Osteonecrosis of the jaw

FDA received reports of several patients with cancer, who were treated with zoledronic acid, who unexpectedly developed osteonecrosis of the jaw (ONJ).[47] In a clinical study reported by Bamias *et al.,*[48] among 252 patients with various malignancies treated with bisphosphonates 17 developed ONJ. The incidence of ONJ increased with time of exposure to the drugs. In another clinical study Marx reported on a series of 36 patients with ONJ who were treated with pamidronate or zoledronic acid.[49] There is higher risk of ONJ in cancer patients who are treated with intravenous bisphosphonates.[50] There is a seven fold increased risk for developing ONJ in the patients with the history of inflammatory dental diseases.[51] Bone imaging techniques may be used for the early identification of ONJ.[50] Some important preventive measures for bisphosphonates-related ONJ include:

1. A routine clinical dental examination before initiating bisphosphonate therapy.
2. Postponing the bisphosphonate therapy until the dental treatment has been carried out. [51-53]

Atrial fibrillation

In a double-blind, placebo-controlled trial, cases of serious atrial fibrillation occurred more frequently in the zoledronic acid group, this was the first indication that intravenous bisphosphonates may cause atrial fibrillation.[54] Another clinical study carried out in America, reported that the risk of atrial fibrillation was greater among women who were treated with alendronate than the women who never used this drug.[55] In contrast, a population based case-control study carried out in Denmark found that the use of bisphosphonates does not increase the risk of atrial fibrillation.[56] Thus, there is some data potentially linking probable association of past bisphosphonate use with an increased risk of atrial fibrillation as a serious adverse event. However the available information does not reveal a consistent association. At the present time, the US Food and Drug Administration (FDA) recommends that physicians do not alter their prescribing patterns for bisphosphonates while it continues to monitor post marketing reports of atrial fibrillation in such patients.[57]

Atypical fractures

Concerns have been raised about potential over suppression of bone turnover during long-term use of alendronate. Patients on long-term treatment with alendronate suffered unusual non-spinal fractures,[58] with severely suppressed bone turnover and metadiaphysial femoral stress fractures, and it was speculated that the patients suffering from these fractures may have osteoclasts genetically susceptible to over-suppression by the bisphosphonates.[59] This is thought to be due to long term over suppression of bone turnover leading to impaired bone remodeling, accumulation of micro damage in bone and increased skeletal fragility.[60-63] These fractures are typically associated with prodromal pain in the region of the fracture and are frequently bilateral; characteristic radiographic findings include cortical hypertrophy, a transverse fracture pattern, and medial cortical spiking.[63] Patients on long-term bisphosphonate therapy should be instructed to consult orthopedic surgeon, if they are experiencing pain or discomfort in the region of the upper thigh or the groin.

Long-term studies with bisphosphonates

In many placebo-controlled trials of 3 and 4 years duration, bisphosphonates have demonstrated anti-fracture efficacy. Fractures reduced within 6 to 12 months of starting therapy with bisphosphonates like zoledronic acid and risedronate. A sustained effect for risedronate has been shown through 5 to 8 years. Besides, 10 years data with alendronate indicated good tolerability and safety. Bisphosphonates accumulated in the bone creates a reservoir leading to continued release from bone for months or years after treatment is stopped. Clinical studies carried out on risedronate and alendronate suggest that if treatment is stopped after 3 to 5 year, there is persisting anti-fracture efficacy, at least for 1 to 2 years. Even after patients stop taking the medication beyond that period, the presence of the medication in the bones continues to keep them healthy and strong. Watt and Diab recommended a drug holiday after 5 to 10 years of bisphosphonate treatment. Treatment duration and holiday length are based on fracture risk and pharmacokinetics of the bisphosphonate used. Patients at mild risk might stop treatment after 5 year and remain off as long as bone mineral density is stable and no fractures occur. Patients at higher risk should be treated for 10 years, have a holiday of no more than 1 to 2 years, and during the drug holiday period these patients must be on a non bisphosphonate treatment.[45]

Calcitonin

Another antiresorptive agent approved for treatment of osteoporosis is calcitonin. Calcitonin acts like the endogenous form of the hormone on the calcitonin receptor on osteoclasts to decrease their activity. Out of all recombinant or synthetic calcitonins that have been used for medical purposes, the salmon calcitonin preparation (SCT) is the most widely used.[64] SCT as a nasal spray is the most commonly used calcitonin formulation due to its convenience of administration. In 1995 SCT was approved in US as a nasal spray for the treatment of postmenopausal osteoporosis.[64] Clinical trials of SCT nasal spray, taken at a dose of 200 IU/day, have demonstrated a 20% decrease in biomarkers of osteoporosis, a small effect on BMD in the spine (1%-2% increase),[65-67] but a 36% reduced incidence of vertebral fractures in women with pre-existing vertebral fractures.[70] No consistent effect on non-vertebral or hip fractures has been demonstrated. An oral SCT preparation is currently in development for clinical use.[64] As a desirable additional effect, calcitonin has been noted to reduce the pain of clinical vertebral fractures.[68]

Selective estrogen receptor modulators

Conformational changes of the estrogen receptors are blocked by selective estrogen receptor modulators (SERM) such as raloxifene. Results from a three year randomized clinical trial study have shown that the incidence of vertebral fractures in raloxifene treated postmenopausal women was reduced to 30%.[69] Also there was a significant decrease in new cases of breast cancers,[70] as well as a significant reduction in the incidence of cardiovascular events in women with increased cardiovascular risk.[71]

Estrogen replacement therapy

Treatment of osteoporotic women with estrogen replacement therapy to prevent fracture has been controversial. The Women's Health Initiative trial on estrogen replacement therapy was the first large-scale, randomized, controlled study of healthy women aged 50-79 years. The results of this study showed that there was 34% risk reduction for hip and vertebral fractures and also by the end of the study, the incidence of osteoporotic fractures was reduced by 24%. Estrogen therapy has long-term side-effects including vascular events and breast cancer which limit its widespread use.[72,73]

Tibolone

Tibolone is a synthetic steroid hormone drug with estrogenic properties, which exerts its effect by binding to the estrogen receptor. The climacteric symptoms were relieved with tibolone therapy, also there was less breast tenderness and menstrual bleeding as compared to the hormone replacement therapy. With the treatment with tibolone for two years in postmenopausal women, the effect on bone density was comparable with the estrogen replacement therapy.[74,75] In a two year, randomized study, the efficacy and tolerability of tibolone was compared with estradiol plus norethindrone acetate (E2/NETA) for preventing bone loss in postmenopausal women. Each treatment effectively caused increase in BMD of lumbar spine, although the increase in BMD with tibolone was smaller than with the continuous hormone therapy.[76]

Parathyroid hormone

The only anabolic agent currently approved for treatment of osteoporosis is PTH analog. It is available in the form of human recombinant PTH peptide 1−34 (teriparatide), a fragment of PTH that has a similar affinity for PTH receptor-1. Normally in response to low serum calcium, PTH is secreted from parathyroid glands, and acts to increase the concentration of calcium in serum by mobilizing calcium from bone. Pharmacologically, when PTH is administered intermittently at low doses, it has been shown to have predominantly anabolic effects on osteoblasts. PTH initiates bone formation first and only later promotes bone formation, which is indicated by bone turnover markers.[77] In clinical studies, treatment with teriparatide increased BMD in the lumbar column and femur and also reduced the incidences of vertebral fractures and non-vertebral fractures.[78,79] The long term safety and efficacy of PTH have not been evaluated beyond 2 years, so it cannot be prescribed for more than 2 years.[77]

Strontium ranelate

Strontium ranelate, a novel orally active agent, has been developed for the treatment of osteoporosis. It consists of two atoms of strontium and an organic moiety ranelic acid. Strontium ranelate acts by both stimulating bone formation and decreasing bone resorption. In vitro, strontium ranelate has been shown to increase osteoblastic activity, including increasing collagen synthesis and modulating the OPG/RANKL system in favor of OPG, as well as decrease bone resorption by decreasing osteoclast differentiation and resorbing activity, and increasing osteoclast apoptosis. Since 2004 strontium ranelate has been approved for the treatment of osteoporosis in European countries.[80] In a summary of the results of four clinical trials of strontium ranelate, three for treatment of osteoporosis[82-86] and one for prevention,[85] 2 g/day of strontium ranelate resulted in increased BMD at all sites, a 37% reduction in vertebral fractures and a 14% reduction in non-vertebral fractures over three years.[81] More recently, a five-year follow-up of one of the treatment trials demonstrated a 43% reduction in hip fractures and 24% reduction in vertebral fractures.[86]

Denosumab (Inhibitors of RANK signaling)

Denosumab is a fully human monoclonal antibody that was developed using transgenic mouse technology. Denosumab binds with high affinity to RANK ligand which prevents the interaction of RANK ligand with its receptor, RANK, which is present on the surface of osteoclasts and their precursors. Denosumab thus inhibits osteoclast activity, thereby decreasing bone resorption in trabecular and cortical bone.[87-89] In a randomized, double-blind, placebo-controlled trial, treatment with denosumab significantly

Table 1
Efficacy of various anti-osteoporotic drugs in fracture prevention and spine BMD gain

Drugs	Spine BMD gain (%) / fracture reduction (%)
Bisphosphonates	
Alendronate	5-7/ 30-45
Ibandronate	4-6/ 32-43
Risedronate	5-7/ 30-45
Zoledronate	6-9/ ~ 70
Denosumab	3-6/ 55-70
Raloxifene **(SERM)**	1.2-3/ 30-40
Estrogen	3-5/ 35
Calcitonin	1-1.5/ 20-30
Anabolic	
Teriparatide	10-15/ 50-65
Strontium Ranelate	2-4/ 20-35

reduced the risk of vertebral, non-vertebral, and hip fractures in postmenopausal women with osteoporosis. Denosomab effectiveness in reducing the risk of vertebral fractures was regardless of BMD baseline, bone turnover baseline rate and baseline history of fracture.[87-90] For the treatment of postmenopausal women with osteoporosis or who are at high risk of osteoporosis, denosumab was granted marketing authorization by the European commission in May 2010.[88] Denosumab was also approved by US FDA in June 2010.[87]

Drugs under clinical development

Cathepsin K

Cathepsin K is critical for normal osteoclastic bone resorption. The two agents which are under development are balicatib (AAE581) and odanacatib (MK-0822). Clinical trials with these agents have demonstrated increase in hip and lumbar spine BMD, with a significant reduction in bone resorption markers.[91] A newer highly potent cathepsin K inhibitor named relacatib is presently being studied in experimental animals.[92]

Src Kinase Inhibitors

Src kinase is a non-receptor tyrosine kinase and a member of the Src family of protein kinases which plays an important role in activity and survival of osteoclast cells.[93] Osteopetrosis was caused in mouse due to Src inactivation, therefore it clearly indicatedthat Src is an important requirement for osteoclastic bone resoption.[94] In *Src* null mutants, osteoclasts fail to form a ruffled border and do not resorb bone. Saracatinib is a novel orally available competitive inhibitor of Src kinase shown to inhibit bone resorption *in vitro*. In a randomized, double-blind, placebo-controlled, multiple-ascending-dose phase I trial treatment with saracatinib inhibited osteoclast mediated bone resorption in healthy men without any significant adverse effects. The results of this study show that saracatinib has the potential to become an agent for the treatment of osteoporosis.[95]

Emerging therapies

The Wnt/β-catenin pathway regulates gene transcription of proteins important for osteoblast function.[96] Study of the pathway has led to further discovery of inhibitors of Wnt signaling secreted by osteocytes. These include sclerostin and dickkopf 1 protein (DKK1), both of which block binding of Wnt to LRP5 (lipoprotein receptor-like protein 5), thereby inhibiting osteoblast stimulation.[97-98] Monoclonal antibodies designed to block the inhibiting action of both sclerostin and DKK1 are being considered for clinical trials based on promising results in animal models.[99-101] Because both of these molecules appear to be secreted only by bone, it is hoped that they will have fewer systemic adverse effects. Therapies targeted at other molecules in the pathway, for example a small molecule inhibitor of GSK3β,[102] the enzyme which causes degradation of β-catenin in the absence of Wnt signaling, are considered less desirable targets due to their action in many tissues in addition to bone.[103]

CONCLUSION

In our conclusion, if osteoporosis is diagnosed and treated early, osteoporotic fractures may be prevented. Newer bisphosphonates like Zoledronic acid with long dosing intervals, newer SERMs with little non-skeletal adverse effects, Strontium ranelate and Denosomab have been introduced to overcome previous shortcomings. Advancement in cellular and molecular level of bone recycling has revealed some newer targets for the therapy of osteoporosis. Several of the new agents are well-advanced in clinical studies, including, cathepsin K inhibitors and Src Kinase Inhibitors. There is a chance that one of these agents may reach the clinic. The other candidate drugs under pharmacological development are likely to emerge for evaluation in clinical studies in the next few years. Of these, drugs targeting the Wnt-β catenin signaling are likely to be prominent. These agents may also be useful in combination with existing antiresorptive agents, further expanding therapeutic options.

REFERENCES

REFERÊNCIAS

1. Lirani-Galvão AP, Lazaretti-Castro M. Physical approach for prevention and treatment of osteoporosis. Arq Bras Endocrinol Metabol 2010; 54 (2):171-8.
2. Martin RM, Correa PH. Bone quality and osteoporosis therapy. Arq Bras Endocrinol Metabol 2010; 54 (2):186-99.
3. Osteoporosis in Men, http://www.niams.nih.gov/health_info/bone/osteoporosis/men.pdf, 2010.
4. Cauley JA, Robbins J, Chen Z, Cummings SR, Jackson RD, LaCroix AZ *et al*. for the Women's Health Initiative Investigators. Effects of estrogen plus progestin on risk of fracture and bone mineral density: the Women's Health Initiative randomized trial. JAMA 2003; 290:1729-38.
5. Canalis E, Giustina A, Bilezikian JP. Mechanisms of anabolic therapies for osteoporosis. N Engl J Med 2007; 357:905-16.
6. Muchmore DB. Raloxifene: A Selective Estrogen Receptor Modulator (SERM) with Multiple Target System Effects.The Oncologist.2000; 5 (5): 388-392.
7. De Paula FJ, Rosen CJ. Developing drugs to treat osteoporosis: lessons learned? Expert Opin Pharmacother 2010; 11:867-9.
8. Cranney A, Guyatt G, Griffith L, Wells G, Tugwell P, Rosen C *et al*. Meta-analyses of therapies for postmenopausal osteoporosis. IX: Summary of meta-analyses of therapies for postmenopausal osteoporosis. Endocr Rev 2002; 23:570-8.
9. Sambrook PN, Ebeling P. Osteonecrosis of the jaw. Curr Rheumatol Rep 2008; 10:97-101.
10. World Population Prospects: The 2008 Revision Population Database. United Nations Population Division. http://esa.un.org/unpp, 2010.
11. Malhotra N, Mithal A. Osteoporosis in Indians. Indian J Med Res. 2008; 127:263-8.
12. The Asian Audit Epidemiology, costs and burden of osteoporosis in Asia 2009. http://www.iofbonehealth.org/download/osteofound/filemanager/publications/pdf/Asian-audit-09/2009-Asian_Audit.pdf, 2010.
13. Jha RM, Mithal A, Malhotra N, Brown EM. Pilot case-control investigation of risk factors for hip fractures in the urban Indian population. BMC Musculoskeletal Disorders 2010; 11:49.
14. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, Eisman JA *et al*. Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 2009; 20 (11):1807-20.
15. Bhatia V. Dietary calcium intake- a critical reappraisal. Indian J Med Res 2008; 127: 269-273.
16. Vitamin D and Calcium: Update Dietary Reference Intakes. http://www.hc-sc.gc.ca/fn-an/nutrition/vitamin/vita-d-eng.php
17. Pande K.C, Johansen K.B, Helboe AB. Digital X-ray Radiogrammetry: establishment and comparison of Indian female and male normative reference data. J Bone Miner Res 2001; 16 (Suppl 1): M087.
18. Action Plan Osteoporosis. The Osteoporosis Society of India. http://www.iofbonehealth.org/download/osteofound/filemanager/policy_advocacy/pdf/action_plan_osteo.pdf.
19. Cawston TE, Young DA. Proteinases involved in matrix turnover during cartilage and bone breakdown. Cell Tissue Res 2010; 339:221-35.
20. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Report of a WHO Study Group. World Health Organ Tech Rep Ser 1994; 843:1-129.
21. Osteoporosis: review of the evidence for prevention, diagnosis and treatment and cost-effectiveness analysis. Osteoporos Int 1998; 8(4):S1-S88.
22. Sambrook P. Osteoporosis B, Pathology and Pathophysiology. Primer on the Rheumatic Diseases, 13th Edition, Springer New York, 2008. http://www.springerlink.com/content/q1326418384m29t7/fulltext.pdf, 2010.
23. Riggs BL, Melton LJ, O'Fallon WM. Drug therapy for vertebral fractures in osteoporosis: evidence that decreases in bone turnover and increases in bone mass both determine antifracture efficacy. Bone 1996; 18:197S-201S.
24. Garnero P, Hausherr E, Chapuy MC, , Marcelli C, Grandjean H, Muller C *et al*. Markers of bone resorption predicts hip fracture in elderly women: the EPIDOS Prospective Study. J Bone Miner Res 1996; 11:1531-8
25. Miller PD, Baran DT, Bilezikian JP, Greenspan SL, Lindsay R, Riggs BL *et al*. Practical clinical application of biochemical markers of bone turnover: Consensus of an expert panel. J Clin Densitom 1999; 2:323-42.
26. Eghbali-Fatourechi G, Khosla S, Sanyal A, Boyle WJ, Lacey DL, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. J Clin Invest 2003; 111:1120-2.
27. Bord S, Ireland DC, Beavan SR, Compston JE. The effects of estrogen on osteoprotegerin, RANKL, and estrogen receptor expression in human osteoblasts. Bone 2003; 32:136-41.

28. Heaney RP, Recker RR, Saville PD. Menopause changes in calcium balance performance. J Lab Clin Med 1978; 92:953-63.
29. McKane WR, Khosla S, Burritt MF, Kao PC, Wilson DM, Ory SJ *et al*. Mechanism of renal calcium conservation with estrogen replacement therapy in women in early postmenopause - a clinical research center study. J Clin Endocrinol Metab 1995; 80:3458-64.
30. Gennari C, Agnusdei D, Nardi P, Civitelli R. Estrogen preserves a normal intestinal responsiveness to 1,25-dihydroxyvitamin D3 in oophorectomized women. J Clin Endocrinol Metab 1990; 71:1288-93.
31. Riggs BL, Khosla S, Melton LJ. A unitary model for involutional osteoporosis:estrogen deficiency causes both type I and type II osteoporosis in postmenopausal women and contributes to bone loss in aging men. J Bone Miner Res 1998; 13:763-73.
32. Cosman F, Nieves J, Horton J, Shen V, Lindsay R. Effects of estrogen on response to edetic acid infusion in postmenopausal osteoporotic women. J Clin Endocrinol Metab 1994; 78:939-43.
33. Ernst M, Heath JK, Rodan GA. Estradiol effects on proliferation, messenger ribonucleic acid for collagen and insulin-like growth factor-I, and parathyroid hormone-stimulated adenylate cyclase activity in osteoblastic cells from calvariae and long bones. Endocrinology 1989; 125:825-33.
34. Oursler MJ, Cortese C, Keeting PE, Anderson MA, Bonde SK, Riggs BL *et al*. Modulation of transforming growth factor-b production in normal human osteoblast-like cells by 17b-estradiol and parathyroid hormone. Endocrinology 1991; 129:3313-20.
35. Pacifici R. T cells and post menopausal osteoporosis in murine models. Arthritis Res Ther 2007; 9:102.
36. Robbie-Ryan M, Pacifici R, Weitzmann MN. IL-7 drives T cellmediated bone loss following ovariectomy. Ann N Y Acad Sci 2006; 1068:348-51.
37. Gao Y, Grassi F, Ryan MR, Terauchi M, Page K, Yang X *et al*. IFN-g stimulates osteoclast formation and bone loss in vivo via antigen-driven T cell activation. J Clin Invest 2007; 117:122-32.
38. Rauner M, Sipos W, Pietschmann P. Osteoimmunology. Int Arch Allergy Immunol 2007; 143:31-48.
39. Chapuy MC, Arlot ME, Duboeuf F, Brun J, Crouzet B, Arnaud S *et al*. Vitamin D3 and calcium to prevent hip fractures in the elderly women. N Engl J Med 1992; 327:1637-42.
40. Bischoff HA, Stahelin HB, Dick W, Akos R, Knecht M, Salis C *et al*. Effects of vitamin D and calcium supplementation on falls: a randomized controlled trial. J Bone Miner Res 2003; 18:343-51.
41. Trivedi DP, Doll R, Khaw KT. Effect of four monthly oral vitamin D3 (cholecalciferol) supplementation on fractures and mortality in men and women living in the community: randomised double blind controlled trial. BMJ 2003; 326:469.
42. Twiss IM, Pas O, Ramp-Koopmanschap W, Den Hartigh J, Vermeij P. The effects of nitrogen-containing bisphosphonates on human epithelial (Caco-2) cells, an in vitro model for intestinal epithelium. J Bone Miner Res 1999; 14:784-91.
43. Waalen J. Current and emerging therapies for the treatment of osteoporosis. J Exp Pharmacol 2010; 2:121-34.
44. Drake MT, Clarke BL, Khosla S. Bisphosphonates: mechanism of action and role in clinical practice. Mayo Clin Proc 2008; 83:1032-45.
45. Watts N.B, Diab D.L. Long-term use of bisphosphonates in osteoporosis. J Clin Endocrinol Metab 2010; 95:1555-65.
46. Papapetrou PD. Bisphosphonate-associated adverse events. Hormones 2009; 8(2):96-110.
47. Edwards BJ, Gounder M, McKoy JM. Pharmacovigilance and reporting oversight in US FDA fast-track process: bisphosphonates and osteonecrosis of the jaw. Lancet Oncol 2008; 9:1166-72.
48. Bamias A, Kastritis E, Bamia C. Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 2005; 23:8580-7.
49. Marx RE. 2003 Pamidronate (Aredia) and Zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003; 61:1238-1239.
50. Khosla S, Burr D, Cauley J. Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone Na Mineral Research. Editorial. J Bone Min Res 2007; 22:1479-91.
51. American Association of Oral and Maxillofacial Surgeons Position Paper on Bisphosphonate-Related Osteonecrosis of the Jaws, September 25, 2006 http://www.aaoms. org/docs/position_papers/osteonecrosis.pdf.
52. Ruggiero S, Gralow J, Marx RE. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Pract 2006; 2:7-14.
53. Marx RE, Cillo JE, Ulloa JJ. Oral bisphosphonate- induced osteonecrosis: risk factors,prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 2007; 65:2397-410.
54. Black DM, Delmas PD, Eastell R, Reid IR, Boonen S, Cauley JA *et al*. Once yearly zoledronic acid for treatment of postmenopausal osteoporosis. N Engl J Med 2007; 356:1809-22.
55. Heckhert SR, Li G, Cummings SR, Smith NL, Psaty BM. Use of alendronate and risk of incident atrial fibrillation in women. Arch Intern Med 2008; 168:826-31.
56. Sorensen HT, Christensen S, Mehnert F, Pedersen L, Chapurlat RD, Cummings SR *et al*. Use of bisphosphonates among women and risk of atrial fibrillation and flutter: population based case-control study. BMJ 2008; 336:813-6.
57. Update of safety review follow-up to the October 1, 2007, Early communication about the ongoing safety review of bisphosphonates (http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm136201.htm).
58. Odvina CV, Zerwekh JE, Rao ES, Maalouf N, Gottschalk FA, Pak CY. Severely suppressed bone turnover: a potential complication of alendronate therapy. J Clin Endocrinol Metab 2005; 90:1294-301.
59. Visekruna M, Wilson D, McKienan FE. Severely suppressed bone turnover and atypical skeletal fragility.J Clin Endocrinol Metab 2008; 93:2948-52.
60. Mashiba T, Hirano T, Turner CH, Forwood MR, Johnston CC, Burr DB. Suppressed bone turnover by bisphosphonates increases microdamage accumulation and reduces some biomechanical properties in dog rib. J Bone Miner Res 2000; 15:613-20.
61. Visekruna M, Wilson D, McKiernan FE. Severely suppressed bone turnover and atypical skeletal fragility. J Clin Endocrinol Metab 2008; 93:2948-52.
62. Armamento-Villareal R, Napoli N, Diemer K, Watkins M, Civitelli R, Teitelbaum S *et al*. Bone turnover in bone biopsies of patients with low-energy cortical fractures receiving bisphosphonates: a case series. Calcif Tiss Int 2009; 85:37-44.
63. Capeci CM, Tejwani NC. Bilateral low-energy simultaneous or sequential femoral fractures in patients on long-term alendronate therapy. J Bone Joint Surg Am 2009; 91:2556-61.

64. Chesnut CH, Azria M, Silverman S, Engelhardt M, Olson M, Mindeholm L. Salmon calcitonin: a review of current and future therapeutic indications. Osteoporos Int 2008; 19:479-91.
65. Overgaard K. Effect of intranasal salmon calcitonin therapy on bone mass and bone turnover in early postmenopausal women: a dose-response study. Calcif Tissue Int 1994; 55:82-6.
66. Chesnut CH, Silverman S, Andriano K, Genant H, Gimona A, Harris S *et al*. A randomized trial of nasal spray salmon calcitonin in postmenopausal women with established osteoporosis: the prevent recurrence of osteoporotic fractures study. PROOF Study Group. Am J Med 2000; 109:267-76.
67. Chesnut CH, Majumdar S, Newitt DC, Shields A, Van Pelt J, Laschansky E *et al*. Effects of salmon calcitonin on trabecular microarchitecture as determined by magnetic resonance imaging: results from the QUEST study. J Bone Miner Res 2005; 20:1548-61.
68. Ljunghall S, Gardsell P, Johnell O, Larsson K, Lindh E, Obrant K *et al*. Synthetic human calcitonin in postmenopausal osteoporosis: a placebocontrolled, double-blind study. Calcif Tissue Int 1991; 49:17-9.
69. Ettinger B, Black DM, Mitlak BH, Knickerbocker RK, Nickelsen T, Genant HK *et al*. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. JAMA 1999; 282:637-45.
70. Cauley JA, Norton L, Lippman ME, Eckert S, Krueger KA, Purdie DW *et al*. Continued breast cancer risk reduction in postmenopausal women treated with raloxifene: 4-year results from the MORE trial. Multiple outcomes of raloxifene evaluation. Breast Cancer Res Treat 2001; 65:125-34.
71. Barrett-Connor E, Grady D, Sashegyi A, Anderson PW, Cox DA, Hoszowski K *et al*. Raloxifene and cardiovascular events in osteoporotic postmenopausal women: four-year results from the MORE (Multiple Outcomes of Raloxifene Evaluation) randomized trial. JAMA 2002; 287:847-57.
72. Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML *et al*. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Womens Health Initiative randomized controlled trial. JAMA 2002; 288:321-33.
73. Stefanick ML. Estrogens and progestins: background and history, trends in use, and guidelines and regimens approved by the US Food and Drug Administration. Am J Med 2005; 118(12):64-73.
74. Beardsworth SA, Kearney CE, Purdie DW. Prevention of postmenopausal bone loss at lumbar spine and upper femur with tibolone: a two-year randomised controlled trial. Br J Obstet Gynaecol 1999; 106:678-83.
75. Berning B, Kuijk CV, Kuiper JW, Bennink HJ, Kicovic PM, Fauser BC. Effects of two doses of tibolone on trabecular and cortical bone loss in early postmenopausal women: a two-year randomized, placebo-controlled study. Bone 1996; 19:395-9.
76. Roux C, Pelissier C, Fechtenbaum J, Loiseau-Peres S, Benhamou CL. Randomized, double-masked, 2-year comparison of tibolone with 17beta-estradiol and norethindrone acetate in preventing postmenopausal bone loss. Osteoporos Int 2002; 13:241-8.
77. Pleiner-Duxneuner J, Zwettler E, Paschalis E, Roschger P, Nell-Duxneuner V, Klaushofer K. Treatment of osteoporosis with parathyroid hormone and teriparatide. Calcif Tissue Int 2009; 84:159-70.
78. Trevisani VF, Riera R, Imoto AM, Saconato H, Atallah AN. Teriparatide (recombinant human parathyroid hormone 1-34) in postmenopausal women with osteoporosis: systematic review. Sao Paulo Med J 2008; 126:279-84.
79. Vestergaard P, Jorgensen NR, Mosekilde L, Schwarz P. Effects of parathyroid hormone alone or in combination with anti-resorptive therapy on bone mineral density and fracture risk - a meta-analysis. Osteoporos Int 2007; 18:45-57.
80. Neuprez A, Hiligsmann M, Scholtissen S, Bruyere O, Reginster JY. Strontium ranelate: the first agent of a new therapeutic class in osteoporosis. Adv Ther 2008; 25:1235-56.
81. O'Donnell S, Cranney A, Wells GA, Adachi JD, Reginster JY. Strontium ranelate for preventing and treating postmenopausal osteoporosis. Cochrane Database Syst Rev 2006; 3:CD005326.
82. Meunier PJ, Slosman DO, Delmas PD, Sebert JL, Brandi ML, Albanese C *et al*. Strontium ranelate: dose- dependent effects in established postmenopausal vertebral osteoporosis a 2-year randomized placebo controlled trial. J Clin Endocrinol Metab 2002; 87:2060-6.
83. Meunier PJ, Roux C, Seeman E, Ortolani S, Badurski JE, Spector TD *et al*. The effects of strontium ranelate on the risk of vertebral fracture in women with postmenopausal osteoporosis. N Engl J Med 2004; 350:459-68.
84. Reginster JY, Seeman E, De Vernejoul MC, *et al*. Strontium ranelate reduces the risk of non-vertebral fractures in postmenopausal women with osteoporosis: Treatment of Peripheral Osteoporosis (TROPOS) study. J Clin Endocrinol Metab 2005; 90:2816-22.
85. Reginster JY, Deroisy R, Dougados M, Jupsin I, Colette J, Roux C. Prevention of early postmenopausal bone loss by strontium ranelate: the randomized, two-year, double-masked, dose-ranging, placebo-controlled Prevos trial. Osteoporos Int 2002; 13:925-31.
86. Reginster JY, Felsenberg D, Boonen S, Diez-Perez A, Rizzoli R, Brandi ML *et al*. Effects of long-term strontium ranelate treatment on the risk of non-vertebral and vertebral fractures in postmenopausal osteoporosis: results of a five-year, randomized, placebo-controlled trial. Arthritis Rheum 2008; 58:1687-95.
87. US Food and Drug Administration, FDA labeling information - Prolia (denosumab). FDA website, http://www.accessdata.fda.gov/drugsatfda_docs/ label/2010/125320s0000lbl.pdf, 2010.
88. European Medicines Agency (EMA). European Public Assessment Report - Prolia. EMA website [online], http://www.ema.europa.eu/docs/en_GB/document_library/EPAR__Product_Information/human/001120/WC500093526.pdf, 2010.
89. Kostenuik PJ, Nguyen HQ, McCabe J, Warmington KS, Kurahara C, Sun N *et al*. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. J Bone Miner Res 2009; 24:182-95.
90. Cummings SR, San Martin J, McClung rMR, Siris ES, Eastell R, Reid IR *et al*. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009; 361:756-65.
91. Peroni A, Zini A, Braga V, Colato C, Adami S, Girolomoni G. Drug-induced morphea: report of a case induced by balicatib and review of the literature. J Am Acad Dermatol 2008; 59:125-9.
92. Kumar S, Dare L, Vasko-Moser JA, James IE, Blake SM, Rickard DJ *et al*. A highly potent inhibitor of cathepsin K (relacatib) reduces biomarkers of bone resorption both in vitro and in an acute model of elevated bone turnover in vivo in monkeys. Bone 2007; 40:122-31.

93. Horne WC, Sanjay A, Bruzzaniti A, Baron R. The role(s) of Src kinase and Cbl proteins in the regulation of osteoclast differentiation and function. Immunol Rev 2005; 208:106-25.
94. Soriano P, Montgomery C, Geske R, Bradley A. Targeted disruption of the c-src proto-oncogene leads to osteopetrosis in mice. Cell 1991; 64:693-702.
95. Hannon RA, Clack G, Rimmer M, Swaisland A, Lockton JA, Finkelman RD *et al*. Effects of the Src kinase inhibitor saracatinib (AZD0530) on bone turnover in healthy men: a randomized, double-blind, placebo-controlled, multiple ascending dose phase I trial. J Bone Miner Res 2010; 25(3):463-71.
96. Baron R, Rawadi G. Targeting the Wnt/beta-catenin pathway to regulate bone formation in the adult skeleton. Endocrinol 2007; 148:2635-43.
97. Balemans W, Ebeling M, Patel N, Van Hul E, Olson P, Dioszegi M *et al*. Increased bone density in sclerosteosis is due to the deficiency of a novel secreted protein (SOST). Hum Mol Genet 2001; 10:537-43.
98. Balemans W, Patel N, Ebeling M, Van Hul E, Wuyts W, Lacza C *et al*. Identification of a 52 kb deletion downstream of the SOST gene in patients with van Buchem disease. J Med Genet 2002; 39:91-7.
99. Li X, Ominsky MS, Warmington KS, Morony S, Gong J, Cao J *et al*. Sclerostin antibody treatment increases bone formation, bone mass, and bone strength in a rat model of postmenopausal osteoporosis. J Bone Miner Res 2009; 24:578-88.
100. Betts AM, Clark TH, Yang J, Treadway JL, Li M, Giovanelli MA *et al*. The application of target information and preclinical pharmacokinetic/pharmacodynamic modeling in predicting clinical doses of a dickkopf-1 antibody for osteoporosis. J Pharmacol Exp Ther 2010; 333:2-13.
101. Ominsky MS, Vlasseros F, Jolette J, Smith SY, Stouch B, Doellgast G *et al*. Two doses of sclerostin antibody in cynomolgus monkeys increases bone formation, bone mineral density, and bone strength. J Bone Miner Res 2010; 25(5):948-59.
102. Kulkarni NH, Onyia JE, Zeng Q, Tian X, Liu M, Halladay DL *et al*. Orally bioavailable GSK-3alpha/ beta dual inhibitor increases markers of cellular differentiation in vitro and bone mass in vivo. J Bone Miner Res 2006; 21:910-20.
103. Hoeppner LH, Secreto FJ, Westendorf JJ. Wnt signaling as a therapeutic target for bone diseases. Expert Opin Ther Targets 2009; 13:485-96.