DENOSUMAB:
A NEW TREATMENT OPTION FOR OSTEOPOROSIS

REVIEW
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ABSTRACT... Osteoporosis is the most common metabolic bone disease in developed countries. One of its major problems is the long term morbidity and poor quality of life of patients. Receptor activator of nuclear factor-kB, its ligand and osteoprotegrin pathway plays an important role in bone remodeling. Receptor activator of nuclear factor-kB interacts with receptor activator of nuclear factor-kB ligand leading to activation of osteoclasts. Denosumab, a fully monoclonal antibody to receptor activator of nuclear factor-kB ligand prevents its binding to receptor activator of nuclear factor-kB and can effectively suppress the bone loss in osteoporosis. Various clinical studies have shown that Denosumab has good efficacy in decreasing bone resorption and has a favourable safety profile also.

Key words: Osteoporosis, receptor activator of nuclear factor-kB (RANK), Denosumab.

INTRODUCTION

Osteoporosis, referred to as "silent epidemic" is characterized by reduction in bone mass, microarchitectural deterioration of bone tissue which leads to increased risk of fractures. The World Health Organization (WHO) defines osteoporosis as a bone density that falls 2.5 standard deviations (SD) below the mean for young healthy adults of same gender (T score of – 2.5)[1]. A loss of one SD gives rise to an enhanced twofold risk of spine fractures or a 2.5 risk of hip fracture[2]. Long term morbidity and lowered quality of life due to vertebral and hip fractures can be the greatest problem associated with osteoporosis.

ABBREVIATIONS	
BALP	Bone specific alkaline phosphatase
BMD	Bone mineral density
IGF	Insulin like growth factor
M-CSF	Macrophage colony stimulating factor
NTX	Urinary N-telopeptide
OPG	Osteoprotegrin
RANKL	Receptor activator of nuclear factor-*k*B ligand
SD	Standard deviation
TGF	Transforming growth factor
TNF	Tumor necrosis factor
TRAIL	TNF related apoptosis inducing ligand
WHO	World health organization

Osteoporosis is the most common metabolic bone disease in developed countries. In the United States, as many as 8 million women and 2 million men have osteoporosis[1]. Decreased bone mineral density (BMD) and osteoporotic fractures impose a great burden on society and individuals.

PATHOPHYSIOLOGY OF OSTEOPOROSIS

Bone's resistance to fracture is determined by its structural and material characteristics, which are determined by life long remodeling of bone by osteoclastic bone resorption and osteoblastic bone formation[3]. Bone remodeling repairs microdamage within the skeleton thus maintaining its strength and also maintains serum calcium by supplying calcium from the bone skeleton.Bone remodeling is regulated by several circulating hormones, like estrogen, androgens, vitamin D and parathyroid hormone, as well as locally produced growth factors like IGF-I &II, transforming growth factor (TGF) β, interleukins, prostaglandins and members of tumor necrosis factor (TNF) superfamily like Receptor activator of nuclear factor-*k*B ligand (RANKL) which is produced by osteoblasts and activated T cells and is responsible for coupling between osteoblasts, osteoclasts and other marrow cells.

It has a dominant role in regulation of bone resorption and in most cases relies on macrophage colony stimulating factor (M-CSF) as a cofactor for osteoclast differentiation. RANK is the cell membrane receptor for

RANKL present on the osteoclast. RANKL activates RANK and this leads to activation of osteoclasts resulting in activation of several intracellular signal transduction pathways which bind nuclear factor kB causing osteoclast differentiation, cell survival and growth[3].

Osteoprotegrin (OPG) is the human decoy for RANKL which is secreted by osteoblasts and it prevents the bone resorption.The role of RANKL-RANK-OPG pathway in the regulation of bone remodeling has been well documented in preclinical studies. RANKL knockout mice have a total absence of osteoclasts and develop osteoporosis. Also, OPG knockout mice have been shown to develop severe osteoporosis and fractures at a young age. Therefore the administration of recombinant OPG prevents bone loss in ovariectomized rats[4].

But OPG has a short half life and is not specific for RANKL as it reacts with other tumor necrosis factors (TNFs), TNF related apoptosis-inducing ligand (TRAIL). Hence the development of OPG as a therapy for osteoporosis was not pursued due to the above mentioned reasons and also because its potential immunogenicity[5].

Denosumab is a fully human monoclonal antibody to RANKL. It has high affinity for RANKL and prevents the binding of RANKL to RANK. This interaction is more specific than OPG as denosumab does not bind to TNFα, TNFβ, TRAIL and hence does not have the potential for autoimmunization. Denosumab has a much longer half life as compared to OPG which is 32 days at a dose of 1 mg/kg[4]. All these attributes make it an attractive therapeutic agent for osteoporosis.

CLINICAL STUDIES

In a randomized, placebo-controlled phase I study in 49 healthy postmenopausal women, a single subcutaneous injection (ranging from 0.01 to 3.0 mg/kg) of denosumab was administered.[6]. There was a dose dependent rapid (within 12 hours), profound (up to 84%) and sustained (up to 6 months) decrease in bone resorption as reflected by urinary N-telopeptide (NTX) levels. Serum levels of bone specific alkaline phosphatase (BALP) remained stable for the first 2 weeks and then decreased in a dose dependent manner indicating that the effect of denosumab is primarily antiresorptive. Regarding the pharmacokinetics: it were nonlinear with dose. A prolonged absorption phase occurred, with maximum serum concentrations being reached between 5 and 21 days after dosing. Half life ranges from about 20 days at lower dose to around 32 days at higher doses. Denosumab was well tolerated. There was no change reported in the circulating numbers of white blood cells, T or B lymphocytes, immunoglobulins or coagulation factors.

The efficacy and safety of subcutaneous denosumab were evaluated in a randomized, placebo-controlled dose ranging phase 2 study in 412 menopausal women with low BMD (T score of -1.8 to 4.0 at the lumbar spine or -1.8 to 3.5 at the proximal femur) over a period of 12 months. Subjects randomly either received denosumab every three months (at a dose of 6, 14 or 30 mg) or every six months (at a dose of 14, 60, 100 or 210 mg), open label oral alendronate once weekly (at a dose of 70 mg), or placebo. The researchers found that denosumab increased BMD at one year especially in the lumbar spine (3.0 to 6.0 % as compared to 4.6 % increase with alendronate and a loss of 0.8 % with placebo) (P<0.001). Slight gains in the total hip (1.9 to 3.6 % increase as compared to 2.1% increase with alendronate and a loss of 0.6% with placebo) (P<0.001), distal third of radius (0.4 to 0.3% increase as compared to a loss of 0.5% and 2.0% with alendronate and placebo respectively) (P<0.001). The study suggested that denosumab in a dose of 60 mg every 6 months and 30 mg every 3 months showed maximum therapeutic benefits. Adverse events and serious adverse events were similar in character and percentage with denosumab compared with placebo[7].

In a double blind phase 3 study in 1180 postmenopausal women with low BMD (T score $\leqslant$ 2.0 in the lumbar spine or total hip), denosumab (60 mg every 6 months) was compared to alendronate (70 mg weekly) for a period of 12 months. It was seen that denosumab significantly increased BMD as compared to alendronate at the total hip (2.5 % versus 2.6%, p< 0.0001) which was the primary end point. At the other skeletal sites too, denosumab increased the BMD (1.1% in the lumbar spine, 0.6% in the femoral neck, 1.0% in the trochanter and 0.6 % in the distal third of radius; p< 0.001 at all

sites).Adverse events were similar for denosumab and alendronate treated patients. Serious adverse events were similar between denosumab and alendronate for infections (1.5% versus 1.0%, p= 0.61) and malignant neoplasm (1.0% versus 0.9%, p= 1.00)[8].

Another Phase III Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) trial, was done on 7868 women with osteoporosis (lumbar spine or total hip T-score –2.5 to –4.0) who were randomized to receive denosumab 60 mg by subcutaneous injection every 6 months, or matching placebo for three years. Patients also received 1000 mg of elemental calcium and 400 to 800 mg of vitamin D daily. Treatment with denosumab was associated with a 68% reduced risk for new vertebral fracture, and a 69% reduced risk for clinical vertebral fracture ($p < .001$). In addition, the risk for nonvertebral fracture was reduced by 20% ($p = .011$) and the risk for hip fracture was reduced by 40% ($p = .036$). BMD at the lumbar spine increased by 9% over three years and by 6 % at the total hip as compared to placebo ($p<0.0001$). The adverse event profile was similar in both treatment arms. There occurred more falls in the placebo group and more flatulence in the denosumab group. As for the serious adverse events, there were 11 cases of concussions in placebo arm and one in the denosumab group, while erysipelas occurred in seven in denosumab group and none in placebo group[9].

CONCLUSIONS

These data support the significant role that RANKL inhibition plays in decreasing bone loss. Denosumab can rapidly and effectively suppress bone loss and is a promising anti-osteoporotic drug. Denosumab has more profound effects on bone resorption as compared to Bisphosphonates and the complete reversibility of bone remodeling after denosumab can result in quick response of changes in BMD when compared to bisphosphonates. All these clinical trials done with denosumab have shown that the adverse and serious adverse events were similar to placebo reflecting its favorable safety profile, but further investigations are still required to assess its long term safety and efficacy.

The twice yearly dosing can provide improved patient compliance as compared to other medications which need to be given more frequently. Denosumab was approved by FDA in 2010 for postmenopausal osteoporosis and bone loss in patients undergoing hormone ablation therapy for either prostate cancer or breast cancer.

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