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Short Communication

Denosumab: A bone antiresorptive drug

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ARTICLE INFO

Article history:
Received 3 October 2013
Accepted 3 February 2014
Available online 24 March 2014

Keywords:
Antiresorptive
Osteoporosis
Giant cell tumor

ABSTRACT

Bone remodeling is the continuous process by which old bone is removed by bone-resorbing cells, the osteoclasts and replaced by new bone synthesized by bone forming cells, the osteoblasts. Osteoporosis is characterized by a progressive loss of bone mass and microarchitecture, which leads to increased fracture risk. Denosumab, a human monoclonal antibody resembling natural IgG2 immunoglobulin, has antiresorptive activity and is distinguished from other antiresorptive drugs. It mimics osteoprotegerin (OPG) that binds to RANKL and hence does not allow RANKL to bind with RANK receptor, thereby inhibiting osteoclast differentiation, activation and survival exerting primarily antiresorptive action. Denosumab trials have shown its efficacy in postmenopausal women with osteoporosis, unresectable giant cell tumor of bone and significant effect in non-metastatic prostate cancer and delay in the time-to-first skeletal related events (SRE) and subsequent SRE with denosumab than zoledronic acid in patients. It is available as 60 mg/ml in pre-filled syringes and approved for osteoporosis in postmenopausal women (60 mg s.c. twice yearly), unresectable giant cell tumor of bone in adults and skeletally mature adolescents (120 mh s.c. monthly), prevention of skeletal-related events and to increase bone mass in patients at high risk for fracture including androgen deprivation therapy for non-metastatic prostate cancer or adjuvant aromatase inhibitor therapy for breast cancer. Denosumab offers advantages of twice yearly dosing in osteoporosis and monthly dosing in giant cell tumor of bone with its novel mechanism of action and better tolerability.

Introduction

Bone remodeling is the continuous process by which old bone is removed by bone-resorbing cells, the osteoclasts and replaced by new bone synthesized by bone forming cells, the osteoblasts.[1,2] This system is critical for skeletal health and its disruption leads to variety of pathologic conditions including osteoporosis, primary bone tumor and metastatic bone tumor.[3]

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http://dx.doi.org/10.1016/j.mjafi.2014.02.001
0377-1237/

The receptor for activating nuclear factor-κB (RANK), the RANK ligand (RANKL), and osteoprotegerin (OPG) are the major regulators of bone metabolism.[4,5] Bone loss occurs when there is an imbalance between the activity of osteoclasts (bone resorption) and osteoblasts (bone formation). RANKL/OPG ratio is a major determinant of bone mass. RANKL interacts with RANK expressed in osteoclast membrane and promotes differentiation, formation and survival of osteoclast.[3]

Osteoporosis is characterized by a progressive loss of bone mass and microarchitecture which leads to increased fracture risk.[1,6] Bone is a major metastatic site for many solid tumors and bone metastasis. These tumors are responsible for pathologic fractures, spinal cord compression and intractable pain which are commonly referred as skeletal-related events (SREs).[7,8] In the setting of osteoporosis and bone metastases in cancer, the interaction between RANKL, RANK and OPG is disrupted.

Currently the most commonly used drugs for osteoporosis and SREs consequent to bone metastasis are bisphosphonates.[3,4] Bisphosphonates have rare but serious adverse events, such as osteonecrosis of the jaw, atypical fractures and oesophageal cancer.[1,5,8]

Human parathyroid hormone analogue teriparatide (the 1-34 N-terminal fragment of PTH) increases bone mineral density (BMD) in women with postmenopausal osteoporosis. It reduces the risk of vertebral and non-vertebral fractures but do not decrease the incidence of hip fractures in postmenopausal osteoporosis.[2,9]

Other available drugs that reduce bone resorption are selective estrogen receptor modulators like raloxifene and basedoxifene.[2] However, these drugs increase the risk of venous thromboembolic events, fatal stroke in postmenopausal women.[2,5,9]

Denosumab, a human monoclonal antibody resembling natural IgG_2 immunoglobulin, has been reported to have antiresorptive activity and is distinguished from other antiresorptive drugs.

Mechanism of action

Osteoblast produces RANKL which binds to RANK present on osteoclast membrane and stimulate differentiation, activation and survival of osteoclast.[1,3,5] Osteoprotegerin (OPG) is a soluble RANKL-binding protein that binds RANKL, prevents it from combining with RANK on the osteoclast membrane. Denosumab by mimicking endogenous OPG binds to RANKL and hence does not allow RANKL to bind with RANK thereby inhibits osteoclast differentiation, activation and survival exerting primarily antiresorptive action (Fig. 1).[3,10]

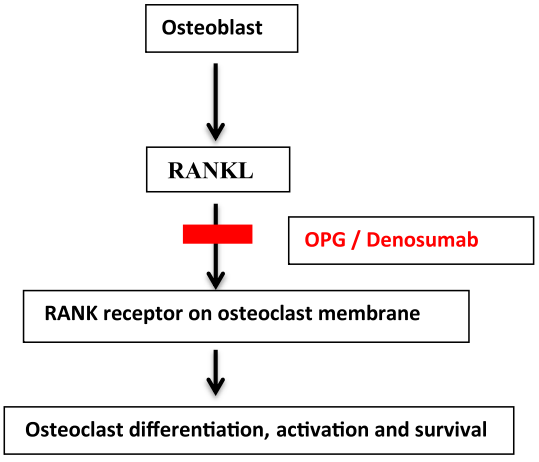

Fig. 1 – Mechanism of action of denosumab.

Pharmacokinetics

Its approved route of administration is subcutaneous (s.c.).[4,7,10] The bioavailability of denosumab after s.c. injection is 61% and its absorption is mediated by lymphatic system.[2,4] Time to reach peak plasma concentration is 10 days after administration of 60 mg and its plasma half-life is 25–38 days.[1] Its effect is reversible. Metabolism of denosumab is unknown and its elimination is through non-specific linear pathway via reticuloendothelial system.[3,10]

Clinical efficacy

Denosumab trial for prevention of fractures in postmenopausal women with osteoporosis (FREEDOM Trial) concluded that it is associated with a reduction in the risk of vertebral, non-vertebral and hip fractures in postmenopausal women with osteoporosis.[5,9]

Two multicentre open-label trials found improved objective response with denosumab in unresectable giant cell tumor of bone by using modified Response Evaluation Criteria in Solid Tumors (RECIST 1.1) which includes tumor shrinkage and time to the development of disease progression.[5,9,11]

Effects of denosumab on BMD and bone turnover in postmenopausal women transitioning from alendronate therapy (STAND Trial) shows that denosumab treatment results in significant increase in BMD in hip, lumbar spine, femoral neck, and distal 1/3rd radius than continued alendronate therapy at 12th month of study.[5,6,8,11]

Two international randomized double-blind, placebo-controlled trials in patients receiving adjuvant aromatase inhibitors therapy for breast cancer or androgen deprivation therapy for non-metastatic prostate cancer shows significant effect on BMD at 12 and 24 months respectively.[9,11] In men with prostate cancer, denosumab also significantly reduced the incidence of new vertebral fractures at 36 months.[11,12]

Three international randomized double-blind double-dummy trials in patients with bone metastases found significant delay in the time-to-first SRE and subsequent SRE with denosumab than zoledronic acid in patients.[9,11]

Placebo controlled Phase-III FREEDOM (Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months) trial, showed significant increase in BMD at the lumbar spine, hip, and distal radius over the three years duration. The mean increase in lumbar spine BMD in the denosumab trials ranged between 3.0% and 5.3% at 12 months, 6.5%–7.7% at 24 months, and 8.2%–10.1% at 36 months of treatment. The mean increase in total hip BMD was 1.6%–3.6% at 12 months, 3.4%–5.1% at 24 months, and 5.2%–6.7% at 36 months. The mean increase in distal radius BMD was 1.1%–1.3% at 12 months and