EDITORIAL

Denosumab-Breakthrough Biological

Sudhaa Sharma*, Shagun Mahajan, Vishal R Tandon***, Annil Mahajan**

Denosumab is a breakthrough biological drug approved by the Food and Drug Administration and European Medicines Agency for the treatment of osteoporosis in 2010. It is a fully human monoclonal antireceptor activator of nuclear factor kappa-B ligand antibody, which inhibits the activity of osteoclasts, resulting in an antiresorptive effect with a significant increase in bone mineral density (1).

The principal regulator of bone resorption is the RANKL/RANK/OPG pathway. RANKL is a transmembrane and soluble protein that is highly expressed by osteoblasts; its receptor, RANK, is located on the cell membrane of osteoclasts and preosteoclasts. RANKL-RANK binding stimulates the formation, activity, and survival of osteoclasts, resulting in increased bone Resorption. OPG is a naturally occurring, soluble, nonsignaling "decoy receptor" for RANKL. By binding to RANKL and preventing its interaction with RANK, OPG inhibits osteoclast formation, activity, and survival, thereby reducing bone resorption (1).Denosumab is a fully human monoclonal antibody of the immunoglobulin G2 isotype with a high affinity and specificity for RANKL. By binding RANKL, denosumab prevents its interaction with RANK, in much the same way as OPG, resulting in a decrease in bone resorption (1).

At 12 months, denosumab treatment is associated with a significant lumbar spine BMD increase of 3.0%-6.7%, depending on the dose and dosing interval, with smaller significant BMD increases observed at other skeletal sites. BMD increases at the total hip and distal one-third radius with subcutaneous denosumab 30 mg every 3 months and 60 mg every 6 months and is greater than with open-label alendronate therapy (2). Treatment with denosumab result in a dose-dependent, rapid, sustained, and reversible suppression of bone turnover markers. In postmenopausal women, a single administration of denosumab result in rapid (within 12 hours), marked (80%), and sustained (6 months) suppression of osteoclast activity (3).

Continuous denosumab treatment for 48 months increase BMD at the lumbar spine (9.4%-11.8% compared with baseline) and total hip (4.0%-6.1% compared with baseline), with consistent suppression of bone turnover markers for the duration of the study. Discontinuation of denosumab after 24 months of treatment is associated with a BMD decrease of 6.6% at lumbar spine and 5.3% at total hip within 12 months of discontinuation (4,5).

In ***DEFEND*** (*Denosumab Fortifies Bone Density*) , a Phase III trial, Denosumab significantly increased BMD at lumbar spine compared with placebo at 24 months to 6.5% (6)

Similarly, In ***DECIDE*** (*Determining Efficacy: Comparison of Initiating Denosumab Versus Alendronate*) Phase III double-blind, double-dummy noninferiority trial, BMD increased more with denosumab compared with alendronate at total hip (denosumab 3.5% versus alendronate 2.6%).There was a statistically significant greater reduction in bone turnover markers with denosumab compared with alendronate (7).

STAND (*Study of Transitioning from Alendronate to Denosumab*) trial suggested discontinuing denosumab

From the PG Deptt. of G. Medicine,*Gyan & Obst, ***Pharmacology &Therapeutics GMC, Jammu, ** ASCOMS, Jammu, J&K
Correspondence to : Dr Annil Mahajan, Proffessor, PG Department of G. Medicine, Govt Medical College, Jammu J&K-India.

(at a dose of 210 mg) after 24 months resulted in a decrease in BMD in the following year comparable to the gains in BMD with 24 months of therapy (8).

FREEDOM (*Fracture Reduction Evaluation of Denosumab in Osteoporosis every 6 Months*), a large 3-year Phase III clinical trial reported treatment with denosumab to be associated with a statistically significant 68% reduction in the risk of new vertebral fractures compared with placebo, 40% reduction in the risk of hip fractures and 20% reduction in the risk of nonvertebral fractures (9).

Denosumab has been approved for treatment of postmenopausal osteoporosis, as the data of clinical trials showed antifracture efficacy of denosumab to be at least as good as current therapeutic agents in the treatment of postmenopausal osteoporosis and is associated with excellent tolerability (1).

It may be particularly important for patients with gastrointestinal contraindications or side effects with oral bisphosphonates and for patients with malabsorption. The long dosing interval of 6 months is likely to be attractive to patients who have difficulty with the more frequent and sometimes bothersome requirements for oral bisphosphonate therapy.

Some advantages proposed for the drug are that it does not accumulate in skeletal tissue , fracture reduction efficacy at multiple sites including spine, nonvertebral, and hip. However, few concern regarding possible adverse effects on the immune system and marked suppression of bone remodeling remain to be evaluated in future trials.

Thus, Denosumab is a promising and emerging drug for the prevention and treatment of postmenopausal osteoporosis and long term safety and efficacy is unknown

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