Editorial

Individualized Dosing of Denosumab for the Treatment of Osteoporosis -

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Denosumab is a potent monoclonal antibody which inactivates the RANK ligand. Inactivation of RANK ligand leads to the inhibition of osteoclast activity and maturation which decreases bone resorption. Denosumab is a potent antiresorptive that has been shown to dramatically suppress bone turnover markers, maintain bone mineral density, and prevent fractures [1]. In postmenopausal women with osteoporosis 60 mg of subcutaneous denosumab given every 6 months reduces the risk of hip fractures by approximately 40% and vertebral fractures by 68% compared with placebo [1]. Denosumab has also shown efficacy and is approved for treatment of osteoporosis in men, treatment of androgen deprivation-induced bone loss in men with prostate cancer, and the treatment of aromatase inhibitor-induced bone loss in women with breast cancer [2,3].

The benefits of denosumab are clearly evident in clinical trials but there are some concerns remain. As with all other antiresorptive agents atypical fractures of the femur are an especially concerning adverse effect. Atypical fractures are thought to be related to over suppression of bone turnover. The exact risk of atypical fractures in patients receiving denosumab is unknown. However there are several published cases of atypical fractures in patients receiving denosumab [4,5]. With bisphosphonates the risk of atypical femur fracture increases with prolonged use. To reduce the risk of atypical femur fractures bisphosphonates are typically not continued longer than 3–10 years depending on fracture risk. Unlike bisphosphonates denosumab is given every 6 months without interruption. In theory there is no end point to the treatment of osteoporosis with denosumab. Some theorize that since the antiresorptive effects of denosumab are shorter than bisphosphonates there will be less risk of atypical fractures. Others think that since denosumab is a more potent inhibitor of bone turnover and requires twice yearly dosing without interruption it may cause more atypical fractures. Clinicians using antiresorptive agents strive to provide treatments that maintain bone mineral density and prevent fractures while avoiding the over suppression of bone turnover.

Bone turnover is highly individualized and influenced by many different factors including renal function, sex hormone concentrations, activity level, and comorbid conditions like hyperthyroidism among others. It would seem reasonable to individualize denosumab dosing based off a particular patient’s bone physiology. One could use bone turnover markers, bone mineral density as provided by DXA scan along with clinical judgement to help decide when subsequent doses of denosumab are necessary instead of giving 60 mg every 6 months. After patients receive their initial dose of denosumab a reasonable approach would be to give another dose of denosumab when one of three events occur: when bone turnover markers are not suppressed by 30–50% of baseline values, BMD declines, or a fracture occurs. A clinician may also opt to give another dose of denosumab if the patient is about to undergo situations that will likely cause loss of bone mineral density such as an upcoming surgery that will require a long period of limited weight bearing or for a solid organ transplantation that will require treatment with high dose corticosteroids, for example.

There are several potential advantages to individualizing the dosing schedule of denosumab. The main advantage would be that a repeat dose of denosumab is only given if bone turnover is not suppressed. This would theoretically avoid over suppression of bone turnover and potentially decrease the risk of atypical femur fractures. Randomized controlled trials would need to be done to prove that this theory is correct. Fewer doses of denosumab would also result in less adverse effects including hypocalcemia, eczema, and injection site reactions. Another significant advantage would also be reducing healthcare costs. Since patients would only be getting denosumab when bone turnover markers are unsuppressed payers may avoid the cost denosumab every six months. However, some of the cost savings of this approach would be negated by the cost of monitoring bone turnover markers twice a year.

There are some concerns over lengthening the interval of denosumab dosing to greater than six months. The biggest concern is that bone turnover markers often increase above baseline values when denosumab is discontinued. One study has shown that bone turnover markers may rise above baseline concentrations as soon as 3-6 months after denosumab has been discontinued [6]. There has also been a report of several cases of severe spontaneous vertebral fracture after discontinuation of denosumab [7]. The authors of this report theorize that these vertebral fractures occurred due to a rebound effect where bone turnover greatly increases above baseline following discontinuation of denosumab. With individualized dosing of denosumab bone turnover markers would be monitored every 6 months. Patients would be given denosumab if bone turnover markers were not suppressed by 30–50% of baseline values as frequently as every 6 months if needed. Through careful monitoring of bone turnover markers, DXA scan, and with clinical judgement you would avoid a rebound effect where bone turnover greatly increases above baseline following discontinuation of denosumab. Another concern is that bone turnover marker assays can be affected by many factors including age, sex, time of day, food intake, physical activity, fractures, vitamin D level, and assay method [8]. Variability in bone turnover markers can be avoided by measuring the levels in similar conditions and by measuring two-three different bone turnover markers. Bone turnover markers should also be monitored and compared to baseline values (value before patient has received a dose of denosumab) for the individual patient and not based off normal ranges.

Despite the concerns over lengthening the dosing interval of denosumab I do think it would be worthwhile to investigate whether this approach is efficacious. A randomized clinical trial, or something similar, that compares the standard twice yearly program of denosumab to individualized dosing of denosumab. Clinical outcomes to this trial should be BMD, hip, vertebral, and non-vertebral fractures. Adverse events such as atypical fractures, hypocalcemia, eczema, infections should also be reported. Healthcare costs could also be compared.

REFERENCES

