Denosumab vs. Denosumab: One Drug, Two Products, and Two Different Indications

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Authors' disclosures of potential conflicts of interest are found at the end of this article.

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Skeletal integrity in a healthy individual requires a balance between bone formation and bone resorption. In normal bone formation, a balance exists between osteoblastic (bone formation) and osteoclastic (bone resorption) activities. When bone remodeling is disrupted by tumor cells, a significant acceleration of the remodeling process results in osteolytic or osteoblastic bone lesions (Roodman, 2004; Yin, Pollock, & Kelly, 2005; Mundy, 2002).

The receptor activator for nuclear factor kappa B ligand, also known as RANK ligand (RANKL), is the essential protein that acts as the key signal for bone removal. In bone metastases, excess amounts of RANKL disrupt the balance of bone remodeling that leads to bone lesions. In the presence of osteoclastic lesions, osteoblastic activity is suppressed, resulting in unopposed osteoclastic activity at the site of malignant cells. In contrast, osteoblastic metastases occur as the result of overactive osteoblastic activity (Schwarz & Ritchlin, 2007).

In many bone loss occurrences, RANKL activity overwhelms the body's natural defense against bone destruction. Bone metastases and skeletal events are two major complications associated with increased morbidity in cancer patients. An estimated 75% of patients with advanced breast or prostate cancer develop bone metastases, and approximately 350,000 patients with bone metastases die each year in the United States alone. Although skeletal metastasis commonly occurs in breast and prostate cancer, it is also observed with other types of solid tumors as well, including renal, thyroid, lung, and colon cancer (Mundy, 2002; Schwarz & Ritchlin, 2007).

This disruption in the equilibrium of bone remodeling not only significantly impacts patients with cancer, but can lead to bone deterioration, such as osteopenia, leading to osteoporosis in the noncancer population as well. Fractures are a major contributor to health-care costs and can have a detrimental impact on patients' lives. The new National Osteoporosis Foundation (NOF) prevalence data estimate that 44 million Americans—55% of the population over age 50—have osteoporosis. Both women and men can have osteoporosis, but approximately 80% of the people in the United States with osteoporosis are women; half of these women over the age of 50 will suffer an osteoporotic fracture in their lifetimes (NOF, 2008).

Indications

In 2010, two products with the same generic name were approved by the US Food and Drug Administration (FDA). Denosumab (Prolia) is indicated for the treatment of postmenopausal women with osteoporosis at high risk for fracture (Amgen, 2010a), defined as a history of osteoporotic fracture, or multiple risk factors for fracture; or patients who have failed or are intolerant to other osteoporosis therapy. Denosumab (Xgeva) is indicated for the prevention of skeletal-related events (SREs) associated with bone metastases from solid tumors excluding multiple myeloma. By definition, a skeletal-related event is defined as radiation to bone, pathologic fracture, surgery to bone, or spinal cord compression (Amgen, 2010b).

Denosumab at a Glance

- Denosumab (Prolia) is indicated for the treatment of postmenopausal women with osteoporosis who are at high risk for fracture
- Denosumab (Xgeva) is indicated for the prevention of skeletal-related events associated with bone metastases in breast cancer, prostate cancer, and advanced solid tumors excluding multiple myeloma
- These two products are not interchangeable
- Coadministration with calcium and vitamin D is recommended
- Hypocalcemia should be corrected prior to initiating therapy
- Both products should be removed from the refrigerator and brought to room temperature 15 to 30 minutes prior to administration
- Both denosumab (Xgeva) and denosumab (Prolia) must be administered by a health-care professional (per package insert)

Pharmacology

Denosumab is a fully humanized IgG monoclonal antibody, with high affinity and specificity for RANKL. Denosumab prevents the binding of RANKL to its receptor RANK, thereby inhibiting the process of excessive osteoclastic activity and minimizing further bone destruction at the presence of bone metastases. The bioavailability was 62% after subcutaneous injection. At doses < 60 mg, denosumab has a nonlinear pharmacokinetic profile, while higher doses translate to a dose-proportional increase in exposure. The mean half-life was 28 days. Urine N-telopeptide (uNTx) is a measurement of bone turnover. The level is elevated when excessive bone resorption exists. In a clinical study of patients treated with denosumab, there was a median decrease in uNTx level by 80% at the end of 13 weeks. This compared favorably to patients treated with zoledronic acid (Zometa), which suppressed uNTx level by 68% (Amgen, 2010a; Amgen, 2010b).

Key Denosumab (Xgeva) Trials

STUDY DESIGN

There were three pivotal, phase III, randomized, double-blind, active-controlled noninferiority trials comparing denosumab (Xgeva) with zoledronic acid in advanced breast cancer, castration-resistant prostate cancer, and advanced solid tumors, including multiple myeloma. In all three trials, one group of patients received denosumab (Xgeva) 120 mg subcutaneously with IV placebo every 4 weeks. In the other group, zoledronic acid 4 mg was given IV with subcutaneous placebo every 4 weeks. All patients were encouraged to take supplemental calcium ≥ 500 mg and vitamin D ≥ 400 IU per day. Per protocol, the dose of zoledronic acid was administered based on creatinine clearance. Renal dose adjustment is not required for denosumab (Xgeva). Patients with a history of IV bisphosphonate therapy were excluded from the study. In all three studies, the primary endpoint included time to first on-study SRE. Secondary endpoints included time to first on-study SRE, time to first and subsequent SRE, safety, and tolerability.

TRIAL RESULTS

The first of the three trials was conducted in advanced breast cancer, where 2,046 patients with bone metastases were randomized to receive denosumab (Xgeva) vs. zoledronic acid. Baseline characteristics were similar in both groups. In each group, 37% had prior history of a SRE. Prior use of IV bisphosphonates was excluded, but 4% received prior oral bisphosphonates. Stopeck et al. (2010) found that the zoledronic acid group had a median 26.4 months until time to first SRE while the median time has not yet been reached for the denosumab (Xgeva) group. The study concluded that denosumab (Xgeva) significantly delayed time to first SRE by 18% vs. zoledronic acid (HR = 0.82; 95% CI = 0.7–0.95; $p < .001$ noninferiority; $p = .01$ superiority). Denosumab

(Xgeva) reduced the risk of developing multiple SREs by 23% compared with zoledronic acid (HR = 0.77; 95% CI = 0.66–0.89; p = .001).

In the second pivotal trial, 1,776 patients with metastatic solid tumors or multiple myeloma were randomized. Fifty percent of the study population had previous SREs. The solid tumors studied included non–small cell lung cancer, multiple myeloma, renal cell carcinoma, and small cell lung cancer, with < 5% of the population representing other tumor types. Henry, Costa, & Goldwasser (2010) concluded no difference until time of first SRE among the two groups (HR = 0.84, 95% CI = 0.71–0.98, p = .06). In a planned subgroup analysis excluding the multiple myeloma population, a 19% risk reduction in time to first SRE was detected, with p = .034 demonstrating significance for noninferiority comparison. A further analysis including patients with both metastatic solid tumors or multiple myeloma showed no difference in time to first and subsequent SRE with a HR = 0.90 (95% CI = 0.77–1.04), p = .145.

In the last head-to-head trial, 1,904 castration-resistant prostate cancer patients with bone metastases were randomized. Baseline characteristics were similar. Approximately 25% of the patients had a prior SRE. Denosumab (Xgeva) had a median time to first SRE of 20.7 vs. 17.1 months with zoledronic acid, which was a 3.6-month difference. Fizazi et al. (2010) found an 18% reduction in time to first SRE, with HR = 0.82 (95% CI = 0.71–0.95), p = .008 demonstrating superiority vs. zoledronic acid. There was an 18% risk reduction in time to first and subsequent SRE.

Summarizing the data for all three pivotal trials, denosumab (Xgeva) superiority in time to first SRE was demonstrated in metastatic breast cancer and metastatic castration-resistant prostate cancer. In the metastatic solid tumors and multiple myeloma trial, denosumab (Xgeva) was shown to be superior when the myeloma patients were excluded. Therefore, denosumab (Xgeva) has received an indication for the prevention of SREs associated with bone metastases from solid tumors excluding multiple myeloma. Overall survival and progression-free survival were similar in all trials comparing denosumab (Xgeva) vs. zoledronic acid (Lipton, Siena, & Rader, 2010).

Pivotal Denosumab (Prolia) Study

The pivotal 3-year phase III trial that demonstrated the safety and efficacy of denosumab (Prolia) in the treatment of postmenopausal women with osteoporosis at high risk for fracture included 7,808 women, aged 60 to 91 years, who had a baseline bone marrow density (BMD) T score between -2.5 and -4.0 at either the lumbar spine or total hip. Patients were randomized to receive subcutaneous injections of either placebo or denosumab (Prolia) once every 6 months. All women received at least 1,000 mg of calcium and 400 IU of vitamin D supplementation daily. Twenty-three percent of the study population had a vertebral fracture at baseline.

Boonen et al. (2011) showed that denosumab (Prolia) significantly reduced the incidence of new vertebral fractures at 1, 2, and 3 years (p < .0001). It was effective in reducing the risk for new vertebral fractures regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture, or prior use of a drug for osteoporosis. The absolute risk of hip fractures was 0.3%, with a relative risk reduction of 40% at 3 years (p = .04). The incidence of hip fracture was 1.2% for the placebo-treated group compared to 0.7% for the denosumab (Prolia)-treated group at year 3. Treatment with denosumab (Prolia) resulted in a 20% reduction in the incidence of nonvertebral fractures as well (p = .01). Denosumab (Prolia) also significantly increased BMD at all anatomic sites measured at 3 years (8.8% at the lumbar spine, 6.4 % at the total hip, and 5.2% at the femoral neck).

Dosing and Administration

For the treatment of postmenopausal women with osteoporosis at high risk for fracture, denosumab (Prolia) 60 mg is given subcutaneously every 6 months; for the prevention of skeletal-related events from bone metastases, denosumab (Xgeva) 120 mg is given subcutaneously every 4 weeks. Patients on denosumab should receive daily concurrent calcium and vitamin D. Since they are marketed under two different brand names, these products are not interchangeable. Prolia is available as a prefilled syringe with a concentration of 60 mg/mL; Xgeva is available as a single-dose vial with a concentration of 70 mg/mL. Both products must be stored in the refrigerator. Prior to administration, both of these products should be removed from the refrigerator and brought to room temperature for 15 to 30 minutes (Amgen, 2010a; Amgen, 2010b).

Table 1. Common Adverse Events Seen With Denosumab (Xgeva) vs. Zoledronic Acid

	Denosumab (Xgeva)	Zoledronic acid
Dyspnea	21%	18%
Hypocalcemia	18%	9%
Hypophosphatemia	32%	20%
Fatigue/asthenia	45%	46%
Nausea	31%	32%
Osteonecrosis of the jaw	1.8%	1.3%

Safety

According to Stopeck et al. (2010), Fizazi et al. (2011), and Henry, Costa, & Goldwasser (2010), the most common serious adverse event associated with denosumab (Xgeva) is dyspnea, but without an increase in acute phase reaction. Other common adverse events are included in Table 1.

As hypocalcemia commonly occurs in the study population, patients are encouraged to receive calcium and vitamin D supplementation. Patients with preexisting hypocalcemia should have it corrected before initiating or continuing with therapy. While osteonecrosis of the jaw remains a rare but serious condition, a proper initial and periodic dental evaluation should be conducted prior to starting denosumab.

Implications

In patients with solid tumors, bone metastasis remains a detrimental complication that is associated with increased morbidity. Therefore, prevention of skeletal-related events in order to minimize the devastating outcomes should be a key goal. As compared to zoledronic acid, denosumab has been shown to be noninferior (primary endpoint) and superior (secondary endpoint) in delaying or preventing SREs. While the safety profiles of these two agents are similar, denosumab does not require adjustment in patients with renal impairment. With the introduction of anti-RANKL agents, advanced practitioners (APs) now have alternative agents in preventing skeletal-related events associated with bone metastases and the treatment of postmenopausal women with osteoporosis at high risk for fracture. Although the mechanism of action is similar in both agents, it is important for APs to recognize the difference in dose and frequency for each of the respective indications. In addition, APs should be aware of the safety aspects associated with these agents. These safety guidelines should be closely followed for patients receiving these products in order to ensure proper administration.

DISCLOSURES

The authors have no conflicts of interest to disclose.

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