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Review Article

Denosumab for the treatment of osteoporosis

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Abstract

Denosumab, a specific inhibitor of RANK ligand, is a novel therapy for postmenopausal osteoporosis and related disorders. An extensive clinical development program has evaluated the clinical efficacy and safety of denosumab with several thousand patients being followed for up to 10 years. Combined with more than six years of postmarketing experience, these studies provide substantial confidence that denosumab is a convenient and appropriate treatment for patients, including Asians, at high risk for fracture. This review will summarize the clinical development of denosumab and lessons learned since its approval for clinical use in 2010.

Keywords: Denosumab; RANK ligand; Osteoporosis; Fracture; Drug safety

1. Introduction

Fractures related to osteoporosis are a major and increasing global health concern. Because the risk of fracture increases with advancing age, the burden of osteoporosis will progressively increase as populations continue to age, especially in Asia where the percentage of the population age 65 years and older is projected to be 9.3% in 2025, an increase of 75% over 1995 [1].

Osteoporosis is the consequence of an imbalance in bone remodeling with resorption exceeding formation, resulting in bone loss, damage to skeletal microarchitecture and impaired bone strength. Rates of bone loss are relatively high in the first year following menopause and in elderly men and women. Therapies that decrease osteoclastic bone resorption such as estrogen and bisphosphonates are known to slow or prevent bone loss and to decrease the risk of osteoporotic fracture in postmenopausal women [2,3].

The discovery and elucidation of the pivotal role played by the receptor activator of nuclear factor-kappa B (RANK) ligand pathway in the regulation of osteoclast activity provided new targets for osteoporosis therapy [4]. The interaction of RANK ligand, an osteoblast-derived growth promoter, with its receptor RANK on pre-osteoclasts is required for the differentiation and proliferation of osteoclasts. Absence of RANK ligand in human and in animal models results in low bone resorption and a phenotype of high bone mass [5,6]. Osteoprotegerin (OPG) is a soluble RANK receptor and is also expressed by osteoblasts. By binding to RANK ligand, OPG inhibits the activation of osteoclasts, reduces bone resorption and increases bone mass in rats and monkeys [7,8]. Based on this understanding and a very strong preclinical platform, denosumab emerged as the first inhibitor of RANK ligand (RANKL) to be registered as a treatment for osteoporosis [9]. This article will review the clinical development of denosumab and studies pertaining to its use in clinical practice.

2. Clinical development

Denosumab is a fully human IgG_2 antibody that avidly and very specifically binds RANKL [9]. In a Phase 1 study, single

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doses of denosumab ranging from 0.01 to 3 mg/kg, were administered to healthy postmenopausal women [10]. Non-linear pharmacokinetics were observed; larger doses were cleared more slowly than smaller doses. As with other human antibodies, clearance is by the reticuloendothelial system, and there is no renal excretion. The acute effects on bone resorption, as measured by reduction in urinary N-telopeptide (NTX), were similar among all doses with decreases of about 80% occurring within 24 h of dosing. The duration of the inhibition of bone resorption was dose-dependent with effects of doses of 60 mg and higher persisting for at least six months. These data confirmed that denosumab functions like OPG to reduce bone resorption by inhibiting the actions of RANKL.

In a Phase 2 dose-ranging study, denosumab was administered subcutaneously range from doses of 6 mg every 3 months to 210 mg every six months (Q6M) to women with low bone mineral density (BMD) [11]. Significant increases in BMD occurred with all doses. With all but the smallest doses, the BMD response in the lumbar spine with denosumab was similar to the response seen in women who had been randomized to receive alendronate 70 mg each week. The increases in BMD in the proximal femur and mid-radius were modestly greater with denosumab than with alendronate. All doses of denosumab resulted in a similar prompt and marked decrease in serum C-telopeptide (CTX) (a marker of bone resorption), decreasing by 85% at three days after dosing with the nadir of the effect occurring at about one month. Again, the duration of the effect on bone resorption was dose-related. Upon dosing with 60 mg denosumab, Q6M, serum CTX gradually increased during the 6 months between doses, reaching a level similar to that observed in women receiving continuous alendronate therapy. Markers of bone formation decreased after 2−3 months of treatment, and the response to denosumab paralleled that seen with alendronate therapy. Similar effects on bone remodeling markers were observed over 8 years of dosing with 60 mg denosumab Q6M [12−15]. The results of the Phase 2 study led to the choice of 60 mg Q6M as the clinical dose to be evaluated in subsequent studies evaluating the effectiveness and safety of denosumab for treatment of postmenopausal osteoporosis.

The pivotal Phase 3 fracture endpoint trial, called the Fracture Reduction Evaluation of Denosumab in Osteoporosis (FREEDOM) study, enrolled 7808 healthy postmenopausal women with osteoporosis who were randomly assigned to receive placebo or denosumab 60 mg subcutaneously Q6M [16]. All received calcium and vitamin D. The average age of subjects in FREEDOM was 72.3 years; 23% had one mild vertebral fracture at baseline. After three years of treatment, the incidence of new morphometric vertebral fractures decreased from 7.2% with placebo to 2.3% with denosumab (68% relative reduction, 95% confidence interval (CI) 59%,74%). A decrease of at least 60% was also seen at the 1 and 2-year time points. The incidence of hip and nonvertebral fracture was 1.2% and 8.0%, respectively, in subjects receiving placebo, and was 0.7% and 6.5%, respectively, in the denosumab group, resulting in a relative risk reduction of hip fracture of 40% (CI 3%,63%) and 20% (CI 5%,33%) for nonvertebral fracture. As was observed in the Phase 2 study, significant increases in BMD were noted in the lumbar spine (9.2%), total hip (6%) and distal radius (3.2%) with denosumab compared to placebo at 3 years [16,17] (Table 1). In FREEDOM, the change in total hip BMD from baseline to 36 months with denosumab accounted for 35% and 87% of the reduction in risk of vertebral and non-vertebral fractures, respectively [18].

The effectiveness of denosumab was evaluated in predefined subgroups of baseline age, body mass index, geography, BMD, fracture status and renal function [19]. The effect of therapy on vertebral fractures did not significantly differ for any of the subgroups analyzed ($p > 0.09$ for all potential interactions). The risk of non-vertebral fracture was statistically significantly reduced in women with a baseline femoral neck BMD T-score ≤ -2.5 but not in those with a T-score > -2.5; in those with a body mass index (BMI) ≤ 25 kg/m^2 but not >25 kg/m^2; and in those without but not with a prevalent vertebral fracture. The effects of denosumab on increasing bone density and decreasing the incidence of vertebral fracture were similar across the spectrum of baseline renal function [20]. This included a total of 2817 women with estimated glomerular filtration rate (GFR) between 30 and 59 mL per minute and 73 women with estimated GFR or 15−29 mL per minute. The efficacy and safety of denosumab therapy in patients with renal failure on dialysis have not been adequately studied.

The incidence of new morphometric vertebral and hip fractures in the placebo group of FREEDOM was substantially lower than observed in pivotal trials of other drugs approved for osteoporosis treatment, likely the consequence of the entry criteria of FREEDOM that excluded women with T-score values of <-4 or with more than one mild vertebral deformity

Table 1
Effects of denosumab therapy on fracture risk in FREEDOM.

Fracture	Placebo (%) $N = 3906$	Denosumab (%) $N = 3902$	Absolute risk reduction (%)	Relative risk reduction (%)	P value
Vertebral	7.2%	2.3%	4.9%	68%	<0.001
Non-vertebral	8.0%	6.5%	1.5%	20%	0.01
Hip	1.2%	0.5%	0.5%	40%	0.04
≥ age 75	2.3%	0.9%	1.4%	62%	0.007
Femoral neck T-score ≤ −2.5	2.8%	1.4%	1.4%	47%	0.02
Wrist	2.9%	2.5%	0.9%	15%	0.21
Femoral neck T-score ≤ −2.5	4.0%	2.4%	1.6%	40%	0.03