FRESH FROM THE PIPELINE

Denosumab

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Denosumab

In May 2010, denosumab (Prolia; Amgen) was granted marketing authorization by the European Commission for the treatment of postmenopausal women with osteoporosis who are at increased risk of fracture, and for the treatment of bone loss associated with hormone ablation therapy in men with prostate cancer at increased risk of fracture. Shortly after, in June 2010, denosumab was approved by the US FDA for the treatment of postmenopausal women with osteoporosis at high risk of fracture.

Fractures owing to skeletal disorders characterized by reduced bone strength, such as osteoporosis, are a major cause of disability, and contribute substantially to health-care costs[1]. The risk of osteoporotic fractures increases with age, particularly in postmenopausal women, in part owing to associated changes in levels of hormones that have a key role in the regulation of bone metabolism[1,2]. Patients receiving hormone-ablation therapy for cancer also have an increased risk of fractures[3].

Bone is continually broken down and replaced through the interplay between the actions of osteoclasts, which mediate resorption of old bone, and osteoblasts, which mediate bone formation[2,4]. Nearly all current drugs for bone-loss disorders such as osteoporosis primarily act by targeting the bone-resorbing activity of osteoclasts, including bisphosphonates, which are the current standard therapy[2,4,5]. Although bisphosphonates can substantially reduce fracture risk, there is still a major need for therapies that can reduce this risk further, as well as for therapies that could help improve adherence; for example, for patients who are intolerant to current drugs.

Basis of discovery

In the past 15 years, it has been shown that the interaction between a cytokine known as receptor activator of nuclear factor κB (RANK) ligand and its receptor RANK on the surface of osteoclasts and their cellular precursors has a key role in osteoclast formation, function and survival[4,6]. Targeting of RANKL–RANK signalling to decrease bone resorption by osteoclasts in disorders such as osteoporosis has therefore been investigated, which led to the development of denosumab.

Drug properties

Denosumab is a fully human immunoglobulin G2 monoclonal antibody that was developed using transgenic mouse technology[7–9]. It binds with high affinity and specificity to RANK ligand, preventing interaction with its receptor, RANK, on the surface of osteoclasts and their precursors[7–9]. Denosumab thus inhibits osteoclast formation, function and survival, thereby decreasing bone resorption and increasing bone mass and strength in cortical and trabecular bone[7–9].

Clinical data

The efficacy and safety of denosumab (60 mg as a subcutaneous injection once every 6 months) for the treatment of postmenopausal osteoporosis were investigated in a 3-year, randomized, double-blind, placebo-controlled trial involving 7,808 women who had a baseline bone mineral density (BMD) T-score between –2.5 and –4.0 at either the lumbar spine or total hip[7,8,10]. All women also received at least 1,000 mg calcium and 400 IU vitamin D supplementation daily[7,8,10]. The primary efficacy end point was the incidence of new vertebral fractures (diagnosed radiologically) after 36 months; secondary end points included the incidence of hip fractures and non-vertebral fractures after 36 months[7,8,10].

Denosumab significantly reduced the incidence of new vertebral fractures after 12, 24 and 36 months compared with placebo[7,8,10]. The incidence of new vertebral fractures after 36 months was 2.3% in women receiving denosumab compared with 7.2% for women receiving placebo — an absolute risk reduction of 4.8%[7,8,10]. The effectiveness of denosumab in reducing the risk for vertebral fractures was regardless of age, baseline rate of bone turnover, baseline BMD, baseline history of fracture or prior use of a drug for osteoporosis[7,8,10].

Denosumab also reduced the risk of hip fractures and of non-vertebral fractures compared with placebo[7,8,10]. After 36 months, the incidence of hip fractures was 0.7% for women receiving denosumab compared with 1.2% for women receiving placebo, and the incidence of non-vertebral fractures was 6.5% for women receiving denosumab compared with 8.0% for women receiving placebo[7,8,10].

The efficacy and safety of denosumab (60 mg as a subcutaneous injection once every 6 months) for the treatment of bone loss associated with androgen deprivation were investigated in 1,468 men with non-metastatic prostate cancer receiving androgen-deprivation therapy[8,11]. The men enrolled were at increased risk of fracture (defined as > 70 years of age, or < 70 years of age with a BMD T-score at the lumbar spine, total hip, or femoral neck < –1.0, or a history of an osteoporotic fracture), and all men received at least 1,000 mg calcium and 400 IU of vitamin D supplementation daily[8,11]. The primary efficacy end point was percent change in BMD at the lumbar spine after 24 months; secondary end points included percent change in BMD at the femoral neck and total hip after 24 months and at all three sites at 36 months, as well as the incidence of new vertebral fractures[8,11].

After 24 months, BMD at the lumbar spine for patients in the denosumab group had increased by 5.6%, compared with a loss of 1.0% in the placebo group[8,11]. After 36 months, the BMD difference between the denosumab and placebo groups was 7.9% at the lumbar spine, 4.9% at the femoral neck, and 5.7% at the total hip[8,11]. Patients receiving denosumab had a decreased incidence of new vertebral fractures after 36 months — 1.5% compared with 3.9% for patients receiving placebo[8,11].

Indications

Denosumab is approved by the FDA for the treatment of postmenopausal women with osteoporosis at high risk for fracture[7]. Denosumab is approved by the European Commission for the treatment of osteoporosis in postmenopausal women at increased risk of fractures and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures[8]. ▸

ANALYSIS | OSTEOPOROSIS

Analysing issues for the treatment of osteoporosis is René Rizzoli, M.D., Chairman of the Department of Rehabilitation and Geriatrics at the Teaching Hospital of Geneva, Switzerland.

Osteoporosis affects a large proportion of the aged population in regions with a prolonged life expectancy; approximately 1 out of 2 women and 1 out of 5 men in such regions suffer an osteoporotic fracture after the age of 50 (REF. 12). Osteoporotic fractures are associated with increased mortality and with long-term disabilities, and thus a major task in the care of the ageing population is to prevent fractures. General measures to achieve these goals target risk factors for osteoporosis that are common in older people, and include dietary supplementation with vitamin D and correcting undernutrition.

However, these measures do not abolish osteoporotic fracture risk, indicating that more powerful approaches, such as pharmacological agents, are needed for patients at increased or high risk of fracture. To identify those patients with an increased risk of fracture, a major step forward has been accomplished with the development of the FRAX tool (http://www.sheffield.ac.uk/FRAX)[13]. This algorithm integrates a few easily recorded clinical risk factors and gives an estimate of the 10-year risk for the so-called major fractures (spine, wrist, humerus and hip) or for hip fracture only, providing key information for input into recommended intervention thresholds[14].

Among the various pharmacotherapies that can reduce the risk of fractures, the bisphosphonates have become the first-line treatment[5]. However, despite new tools to identify patients at increased risk of fractures and the availability of effective drugs, many such patients are not receiving therapy. In part, this is due to insufficient disease awareness among both physicians and patients, but a major problem is also the low adherence to treatment, which is probably related to the inconvenience of administration regimens and tolerability issues. For instance, adherence to oral formulations of bisphosphonates is less than 50% within a year after starting therapy[15], and importantly, with compliance lower than 50%, there is no reduction in fracture risk from treatment[16].

The recent approval of the monoclonal antibody denosumab has provided a highly efficacious addition to the armamentarium of treatments for osteoporosis. Denosumab markedly decreases the rate of bone remodelling, even in patients who have previously received bisphosphonates[17], and reduces the incidence of fracture in the spine and peripheral skeleton, including the proximal femur. The magnitude of the antifracture efficacy is at least as high as the most efficacious bisphosphonate. In addition, denosumab is given subcutaneously every 6 months, thus avoiding the inconvenience of the oral or intravenous formulations. Further studies will clarify the extent of the potential for denosumab in other groups of patients at risk of fractures, such as cancer patients receiving hormone ablation therapy.

Box 1 | The market for drugs for bone-loss disorders

Analysing the market for bone-loss disorders is Uma Yasothan, IMS Health, London, UK.

The current standard of care for the treatment of postmenopausal osteoporosis (PMO) is the bisphosphonate class of drugs. In 2009, the global bisphosphonate market was worth ~US$8 billion, with ibandronate (Boniva; Roche) and zoledronate (Zometa; Novartis) holding 25% and 19% share of this market across all indications, respectively, and showing an average sales growth rate of ~21% in the past 2 years[18]. Denosumab (Prolia; Amgen) is the latest entrant to the PMO treatment market, following its approval for this indication in the United States and the European Union (where it also approved for bone loss associated with hormone ablation therapy in men with prostate cancer). Denosumab is ultimately anticipated to compete directly with the bisphosphonates, although initial uptake is likely to be as second-line and third-line therapy, mostly in patients who are intolerant or unresponsive to bisphosphonates. The subcutaneous administration of denosumab might also help favour uptake compared with long-acting bisphosphonates, which need intravenous administration.

In addition to the treatment of PMO, there is substantial potential for denosumab for treating bone loss in patients with cancer, for which Zometa finds a wider use as the only bisphosphonate currently approved. In 2009, sales for Zometa in oncology indications were $1.5 billion, representing 75% of the global sales of this drug[18]. Further clinical trial data for denosumab in oncology indications are expected in the third quarter of 2010, including head-to-head comparisons with Zometa, which could increase the potential market for denosumab considerably if they are positive. Analysts' sales expectations for denosumab currently range from $100 million globally in 2010 (REF. 19) to >$1 billion by 2013 (REF. 20) for the PMO indication in the United States.

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Competing interests statement
R. R. declares competing financial interests: see web version for details.

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