



Denosumab

a new treatment for postmenopausal osteoporosis

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Denosumab (Prolia) is a promising new first-line agent for the treatment of postmenopausal osteoporosis with proven fracture risk reduction.

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WHAT IS DENOSUMAB?

Postmenopausal osteoporosis results from an imbalance between bone resorption and formation, favouring the former. Osteoclastic bone resorption is principally regulated by the interaction of receptor activator of nuclear factor- κ B ligand (RANKL) and its receptor on osteoclasts and osteoclast precursors. Osteoprotegerin is an endogenous decoy receptor for RANKL. Acting in a similar manner to osteoprotegerin, denosumab (Prolia) is a fully human monoclonal antibody to RANKL that prevents its interaction with osteoclasts and, consequently, reversibly inhibits bone resorption by reducing both osteoclast formation and differentiation, and increasing osteoclast apoptosis.

WHEN IS IT USED?

A three-year, double-blind, randomised, placebo-controlled trial involving 7868 postmenopausal women with osteoporosis has shown that 60 mg denosumab given as a subcutaneous injection every six months increases the bone mineral density (BMD) at the lumbar spine and hip. There were also associated significant relative risk reductions for fractures at vertebral (68%), nonvertebral (20%) and hip (40%) sites.^{1,2} Additionally, comparison trials with alendronate have demonstrated greater increases in BMD at all sites with denosumab.²⁻⁴

Denosumab was listed on the PBS from 1 December 2010 indicated as the sole-subsidised antiresorptive agent for the treatment of osteoporosis in women aged 70 years or older with a BMD T-score of -3.0 or less, and/or for the treatment of established postmenopausal osteoporosis in patients with fracture due to minimal trauma. With the addition of denosumab as a therapeutic alternative for postmenopausal osteoporosis, there is increased scope to tailor specific treatment regimens for patients. When compared with other available agents, the benefits of denosumab include the absence of gastrointestinal side effects that may limit oral bisphosphonate use and the ease of administration by family doctors that may lead to improved compliance rates (Table).

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TABLE. AGENTS FOR THE TREATMENT OF POSTMENOPAUSAL OSTEOPOROSIS

Generic name	Denosumab	Alendronate	Risedronate	Strontium ranelate	Zoledronic acid	Teriparatide
Trade name	Prolia	Fosamax	Actonel	Protos	Aclasta	Forteo
Class	RANK ligand inhibitor	Bisphosphonate	Bisphosphonate	Not applicable	Bisphosphonate	Recombinant human parathyroid hormone
Administration	Subcutaneous, 60 mg per six months	Oral, 70 mg per week	Oral, 35 mg per week or 150 mg per month	Oral, 2 g per day	Intravenous, 5 mg per year	Subcutaneous, 20 µg per day
Limitations	Lacks long-term data	Gastrointestinal side effects Compliance	Gastrointestinal side effects Compliance	Increased deep vein thrombosis Compliance	Intravenous Lacks long-term data	Restricted use Lacks long-term data
Advantages	Compliance	Long-term data	Long-term data	Long-term data	Compliance	Anabolic

HOW IS IT USED?

Denosumab is packaged as a 60 mg in 1 mL single-use prefilled syringe.⁵ Denosumab 60 mg is injected subcutaneously into the upper arm, upper thigh or abdomen of patients by a healthcare professional every six months. All patients receiving denosumab should receive at least 1000 mg calcium daily using diet and/or supplements and 400 IU vitamin D daily.

Dose adjustment is unnecessary in patients with renal impairment because denosumab is not renally excreted. Although no studies have evaluated the effect of hepatic impairment on the pharmacokinetics of denosumab, hepatic impairment is unlikely to have a major effect because clearance of denosumab is by endocytosis or by hepatic macrophages.

WHAT NEEDS MONITORING?

As with all patients receiving antiresorptive agents for osteoporosis, serum calcium and vitamin D levels should be monitored. Low levels must be corrected prior to the administration of denosumab.

COMMON SIDE EFFECTS

Denosumab is well tolerated with adverse effect rates generally similar to placebo.^{1,3,4,6-8}

It is also effective and safe at different levels of renal function.⁹ The most common adverse reactions include musculoskeletal pain, hypercholesterolaemia and eczema. If these side effects are severe, discontinuation should be considered.⁵ Hypocalcaemia may occur, especially in patients with stage 5 chronic kidney disease, and pancreatitis has also been reported in clinical trials. RANKL is expressed on activated T and B lymphocytes and in lymph nodes; therefore, denosumab has the potential to increase the risk of infection and neoplasia. Increased rates of serious skin infections, predominantly cellulitis, have been observed in trials and patients should seek prompt medical attention if they develop signs and symptoms of infection. However, no significant increases in malignancy rates have been noted to date.

Consistent with other antiresorptive agents, denosumab suppresses bone turnover. Osteonecrosis of the jaw has rarely been reported with denosumab and a routine oral examination is recommended prior to commencement.¹⁰ Atypical fractures and delayed fracture healing have not yet been observed in trials with denosumab and the pivotal three-year fracture prevention trial will be continued

as an open-label study out to 10 years to monitor for both efficacy and any potential long-term adverse effects.

IMPORTANT PRECAUTIONS AND INTERACTIONS

As hypocalcaemia may be exacerbated by the use of denosumab, patients with conditions that predispose to hypocalcaemia (e.g. hypoparathyroidism, thyroid surgery, parathyroid surgery, malabsorption syndromes, excision of small intestine, severe renal impairment [creatinine clearance <30 mL/min], renal dialysis) should be made aware of the symptoms of hypocalcaemia and have calcium, magnesium and phosphorus levels monitored regularly. Vitamin D deficiency (<50 nmol/l) should be corrected before commencing treatment with denosumab. Immunosuppressed patients may be at an increased risk for serious infections and therefore the risk-benefit ratio should be assessed on a case-by-case basis.

For patients with risk factors for osteonecrosis of the jaw, such as poor dental hygiene, requirement for invasive dental procedures or a concurrent malignancy, a dental examination with appropriate management is recommended prior to the commencement of denosumab. No

drug–drug interaction studies have been conducted with denosumab. However, it is not recommended that denosumab be used with other monoclonal antibodies (biological medications). It is important to continue treatment at six-monthly intervals due to rapid rebound osteoclast activity and bone loss that occur with longer dosing intervals.⁷

SUMMARY

Denosumab is a promising new first-line agent for the treatment of patients with postmenopausal osteoporosis with proven fracture risk reduction. Advantages of this agent include infrequent subcutaneous dosing intervals without the need for intravenous administration. It is likely to have a particularly important role in patients with either a poor treatment response to or an inability to tolerate other antiresorptive agents. The side effect profile appears very favourable; however, long-term studies are being conducted to monitor efficacy and for potential adverse events. **MT**

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