Therapeutic Brief

**Denosumab for the treatment of osteoporosis**

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**Abstract**

Denosumab is a monoclonal antibody which binds to the receptor activator of nuclear factor-κB ligand (RANKL), reducing osteoclastic activity and bone turnover. The Fracture REduction Evaulation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial showed a significant reduction in relative risk of fractures with increased bone mineral density (BMD) with denosumab. A trial of DenosumAb versus placebo in Males with Osteoporosis (ADAMO) demonstrated the similar effect of denosumab for improving BMD and reducing bone turnover in men. However, concerns were identified regarding increased risk of fractures with denosumab cessation. Until further evidence is available, bisphosphonate treatment is recommended to attenuate this risk with denosumab discontinuation.

**Key Words.** Denosumab; Fractures; Osteoporosis

Denosumab is a fully human monoclonal antibody used for osteoporosis treatment. It has a high affinity and specificity for the receptor activator of nuclear factor-κB (RANK) ligand, a cytokine and mediator of osteoclastic bone resorption. RANK is a receptor on osteoclastic precursors; when RANK ligand binds to this, it promotes differentiation, proliferation and survival of osteoclasts, resulting in increased bone turnover. The discovery of this pathway led to the consideration of new molecular targets for osteoporosis treatment. Denosumab inhibits RANKL, resulting in reduced osteoclastic activity and bone resorption [1]. Although it is administered as a subcutaneous injection every six months, the Denosumab Adherence Preference Satisfaction (DAPS) study showed that 92.4% preferred denosumab over oral alendronate, with associated compliance and satisfaction rates [2].

The landmark trial confirming its benefit in osteoporosis treatment was the Fracture REduction Evaulation of Denosumab in Osteoporosis every 6 Months (FREEDOM) trial. 7808 osteoporotic older women were randomised to denosumab or placebo for 36 months. Denosumab was associated with relative risk reductions of new radiographic vertebral fractures (68%), non-vertebral fractures (20%) and hip fractures (40%) [3]. The extension of the FREEDOM study showed the benefits of denosumab treatment continued for up to ten years in terms of low fracture incidence and increased BMD without plateau, with low rates of adverse events [4]. However, subgroup analyses showed the risk reduction was significant only in women with a baseline femoral neck bone mineral density (BMD) T‐score ≤ −2.5, body mass index (BMI) < below 25 kg/m2 and in those without a prevalent vertebral fracture [5].

The FREEDOM study also showed that denosumab was associated with reductions in serum C‐telopeptide of type I collagen (CTX), a biochemical marker of bone resorption, to below premenopausal reference intervals [6]. There were also improvements in hip and spine strength by 14.3% and 22.4% at 36 months compared to placebo, measured through nonlinear finite element analysis (FEA) of hip and spine quantitative computed tomography (QCT) scans [7]. The increased hip and spine strength was seen in both the trabecular and cortical bone components.

The benefits of denosumab was also demonstrated in men with low BMD in A trial of DenosumAb versus placebo in Males with Osteoporosis (ADAMO). When 228 men were randomised to denosumab or placebo for 24 months, treatment was associated with increased BMD and reduced bone resorption at levels similar to the FREEDOM study [8].

Denosumab was also shown to be more cost-effective for treatment of older men aged above 75 years in two separate studies from Sweden and the United States compared to the other osteoporotic agents, including bisphosphonates and teriparatide. The lifetime cohort Markov model demonstrated that although there is a higher annual treatment cost compared to other medications, denosumab was more cost-effective for osteoporosis treatment in terms of lifetime expected costs and quality-adjusted life-years [9,10].

A meta-analysis identified ten randomised controlled trials comparing the efficacy of denosumab and bisphosphonates. Denosumab was associated with significant improvement in BMD at the lumbar spine, hip and femoral neck at 12 and 24 months compared to bisphosphonates. There was also a lower incidence of osteoporotic fractures for denosumab than alendronate at 24 months [11]. Another trial confirmed a significant improvement in spine and hip BMD with denosumab over risedronate at 24 months for patients with glucocorticoid-induced osteoporosis without any differences in the rate of adverse events [12].

A case series of severe spontaneous vertebral fractures after denosumab discontinuation raised concerns regarding severe osteoporosis rebound with treatment cessation [13]. An observational study found a reversal of BMD benefits and possibly fracture risk, identifying eight (9.8%) patients who experienced 17 fractures within the year [14]. When the FREEDOM study participants who discontinued denosumab were followed-up for up to 24 months, there were similar fracture rates in the denosumab (7%) and placebo (9%) groups, without any differences in fracture occurrence patterns [15]. However, until further evidence is available, it is recommended to assess the risk and benefit of denosumab treatment after five years, and to consider bisphosphonates if denosumab was discontinued to attenuate rebound increases in bone turnover [16]. Further studies are required to explore the optimal duration of prolonged denosumab treatment and which anti-resorptive agent is preferred after discontinuation of denosumab.

Finally, given the possible rebound in fracture risk with denosumab cessation, clinicians should check and emphasise the importance of patient compliance with treatment. A Swedish Prescribed Drug Register identified multiple reasons which may contribute to reduced persistence with treatment including healthcare organization, approaches to drug monitoring and population disease awareness [17]. Thus, as systematic healthcare approach is also required to avoid premature discontinuation of osteoporosis treatment, particularly denosumab.

In summary, denosumab is useful for osteoporosis management, but clinicians should be aware of increased fracture risk with treatment discontinuation.

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