Denosumab for the treatment of osteoporosis

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Abstract

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

Keywords: Denosumab, fracture, osteoporosis
Two separate studies from Sweden and the United States also showed denosumab to be more cost effective than other osteoporotic agents, including bisphosphonates and teriparatide, for treatment of older men aged over 75 years. The lifetime cohort Markov model demonstrated that denosumab had a higher annual treatment cost compared to other medications but was more cost effective for osteoporosis treatment in terms of the lifetime expected costs and quality-adjusted life-years [9, 10]. A meta-analysis identified ten randomized controlled trials that compared the efficacy of denosumab versus bisphosphonates. Denosumab was associated with a significant improvement in BMD at the lumbar spine, hip and femoral neck at 12 and 24 months compared to bisphosphonates. A lower incidence of osteoporotic fractures was also evident for denosumab than for alendronate at 24 months [11]. Another trial confirmed a significant improvement in spine and hip BMD with denosumab versus risedronate at 24 months, with no difference in adverse events, in patients with glucocorticoid-induced osteoporosis [12]. A case series of severe spontaneous vertebral fractures after denosumab discontinuation raised concerns regarding a severe osteoporosis rebound upon treatment cessation [13]. An observational study found a reversal of BMD benefits and a possibly increased fracture risk, as eight (9.8%) patients experienced 17 fractures within the year [14]. By contrast, a 24-month follow-up of the FREEDOM study participants who discontinued denosumab revealed similar fracture rates in the denosumab (7%) and placebo (9%) groups, with no evidence of any differences in the fracture occurrence patterns [15]. However, until further evidence is available, the most prudent recommendation is to assess the risks and benefits of denosumab treatment after five years and, if denosumab is to be discontinued, to consider bisphosphonates 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 preferable after discontinuation of denosumab. Finally, given the possible rebound in fracture risk with denosumab cessation, clinicians should be vigilant and emphasize the importance of patient compliance with treatment. A Swedish Prescribed Drug Register identified multiple reasons that may contribute to reduced adherence to treatment, including the healthcare organization, approaches to drug monitoring, and population disease awareness [17]. Thus, a systematic healthcare approach is also required to avoid premature discontinuation of osteoporosis treatment, and particularly denosumab. In summary, denosumab is useful for osteoporosis management, but clinicians should be aware of the increased fracture risk upon treatment discontinuation.

**Declaration**

**Conflict of Interest:** The authors declare that they have no conflict of interest.

**References**


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