**Title Page:**

**Denosumab for the treatment of osteoporosis**

**(Therapeutic Brief)**

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Running Title:

Denosumab for the treatment of osteoporosis

**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

**Response to Reviewers:**

Please find attached responses to reviewer comments regarding the manuscript. Any changes made to the manuscript are indicated in RED.

Reviewer A:  
  
In this manuscript, the author describes concisely the monoclonal antibody Denosumab and its role in treating osteoporosis, supported by multiple clinical trials throughout the years with potential post-treatment adverse effects. The reviewer suggests the author to expand the discussion of Denosumab in the following areas to make the manuscript better understandable for the audience.  
  
The author should elaborate more on describing the osteoclastogenesis and osteoclastic bone resorption mechanisms; the role of RANKL plays in initiating these pathways, and how Denosumab can inhibit osteoclasts and further bone resorption. A figure would help demonstrating the processes.

Thank you for the suggestion. The following paragraph has been added:

‘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].’

There are several diagrams available to demonstrate the osteoclastogenesis pathway. Unfortunately, it is not possible to reproduce a similar diagram for this manuscript without seeking permission from owners of those diagrams.

In addition, is there a difference in osteoporosis treatment efficiency using Denosumab between man and woman? Even though both man and woman can have osteoporosis, many osteoporosis clinical studies do not include man. As a result, the reviewer suggests the author to investigate more into the  
effect of Denosumab on treating osteoporosis in man compared to woman.

The ADAMO trial in men was mentioned in the manuscript confirming that the efficacy of Denosumab is similar to that obtained in the FREEDOM trial in women. From a health economics perspective, there are also studies showing the cost-effectiveness of denosumab in osteoporosis treatment in men. The following sentence has been added to the manuscript:

‘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].’

The following references were added:

Parthan A, Kruse M, Agodoa I, Silverman S, Orwoll E. Denosumab: a cost-effective alternative for men with osteoporosis from a Swedish payer perspective. Bone 2014;59:105-113.

Silverman S, Agodoa I, Kruse M, Parthan A, Orwoll E. Denosumab for elderly men with osteoporosis: a cost-effectiveness analysis from the US payer perspective. J Osteoporos 2015;2015:627631

Reviewer B:  
  
Therapeutic Brief: “Denosumab for the treatment of osteoporosis” by Shyh Poh Teo  
  
This is a well-written, short review of the dangers of discontinuation of denosumab treatment in patients with osteoporosis. While well written, the reviewer has a few concerns:  
  
• It is unclear to the reader what is the significance or novelty of this review. The author cites “recent” concerns identified regarding increased risk of fractures with denosumab cessation. However, the authors  
does not cite any recent literature later than 2017.

The word ‘recent’ has been removed from the sentence in the abstract, which now reads: ‘However, concerns were identified regarding increased risk of fractures with denosumab cessation.’

• More information regarding the benefits and risks of the treatment with denosumab versus bisphosphonates would be helpful to the general reader. For example, it would be helpful to the reader to know the relative efficacy of the two types of treatments.

Thank you for this suggestion. We have added the following paragraph to clarify the relative efficacy of denosumab versus bisphosphonates:

‘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].’

The following references were added:

Lyu H, Jundi B, Xu C, et al. Comparison of denosumab and bisphosphonates in patients with osteoporosis: a meta-analysis of randomised controlled trials. J Clin Endocrinol Metab 2019;104(5):1753-65.

Saag KG, Pannacciulli N, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: final results of a twenty-four-month randomized, double-blind, double-dummy trial. Arthritis Rheumatol 2019;71(7):1174-1184.

• It would be helpful to the general reader to know what are the reasons for discontinuation of denosumab that would lead to increased risk of fractures, if it is preferred over orally administered bisphosphonate? Is the drug discontinued because of cost, availability or other factors such as  
adverse incidents?

There are multiple reasons for discontinuing denosumab in addition to patient compliance, which is a concern. A study on reduced persistence outlines possible reasons for this. The following paragraph has been added:

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.

The following reference has been added:

Karlsson L, Lundkvist J, Psachoulia E, Intorca M, Strom O. Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: a retrospective, observational study, and a meta-analysis. Osteoporos Int 2015;26:2401-2411.

• Are there any trials that compare the efficacy of bisphosphonates versus denosumab after discontinuation of denosumab treatment? The trials referred to by the author only compare denosumab to placebo.

Unfortunately, the advice to switch to another anti-resorptive agent after discontinuing denosumab treatment is based on expert recommendations. This is stated in the second last paragraph ‘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].’

We have added the following text to explicitly clarify this reviewer’s valid question:

‘Further studies are required to explore the optimal duration of prolonging denosumab treatment and which anti-resorptive agent is preferred after discontinuation of denosumab.’

**Denosumab for the treatment of osteoporosis**

**(Therapeutic Brief)**

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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