


A Review on the Role of Denosumab in Fracture Prevention

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy

Kok-Lun Pang ^{1,*}
Nie Yen Low ^{1,*}
Kok-Yong Chin ^{1,2}

¹Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Kuala Lumpur, Malaysia; ²State Key Laboratory of Oncogenes and Related Genes, Renji-Med X Clinical Stem Cell Research Center, Department of Urology, Ren Ji Hospital, School of Medicine, Shanghai Jiao Tong University, Shanghai 200030, People's Republic of China

*These authors contributed equally to this work

Abstract: Denosumab is a receptor activator of nuclear factor kappa-B ligand inhibitor, which suppresses the bone resorption process to preserve bone mass. It is usually recommended to postmenopausal women and men with high fracture risk. With the recent publication of the results from FREEDOM study and its extension, the long-term effect of denosumab in preventing fragility fractures has been put forward. This review aims at summarising the evidence of denosumab in reducing fracture risk and its safety derived from clinical studies. Most of the evidence are derived from FREEDOM trials up to 10 years of exposure. Denosumab is reported to prevent vertebral and non-vertebral fractures. It is also proven effective in Japanese women, patients with chronic kidney diseases and breast cancer patients receiving antineoplastic therapy. Denosumab discontinuation leads to high remodeling, loss of bone mineral density and increased fracture risk. These negative effects might be preventable by bisphosphonate treatment. The safety profile of denosumab is consistent with increased years of exposure. In conclusion, denosumab is a safe and effective option for reducing fracture risk among patients with osteoporosis.

Keywords: bone mineral density, bone turnover marker, menopause, osteopenia, osteoporosis

Introduction

Osteoporosis is a metabolic disease of the skeletal system with insidious onset and affects bone mineral density (BMD) adversely.¹ According to World Health Organization, osteoporosis is defined as a BMD that lies 2.5 standard deviations or more below the average value for young adult (T-score ≤ -2.5).² Fragility fractures are the ultimate consequence of osteoporosis. An estimate showed that 75% of all vertebral and non-vertebral fractures occur in individuals aged ≥ 65 years, and more than 75% of hip fractures affect individuals aged ≥ 75 years.³ Fragility fractures are traumatic events for the octogenarians and geriatric patients because their overall health and functioning status will be severely impaired.^{4,5} Vertebral fractures were linked with increased comorbidity and admission events, as well as prolonged duration of hospitalization.⁶ Elderly men have higher chances of suffering from these complications, particularly pneumonia and musculoskeletal diseases, compared to their female counterparts.^{7,8} Patients with fragility fracture suffer from higher morbidity, higher risk for subsequent fracture and greater mortality risk after discharge.⁹ Patients with refracture possess a mortality rate of 1.2 times higher than patients without refracture patients 3 years.¹⁰

Correspondence: Kok-Yong Chin
Level 17, Preclinical Building, Department of Pharmacology, Faculty of Medicine, Universiti Kebangsaan Malaysia, Jalan Yaacob Latif, Bandar Tun Razak, Cheras 56000, Kuala Lumpur, Malaysia
Tel +603 9145 9573
Email chinkokyong@ppukm.ukm.edu.my

Both pharmacological and non-pharmacological strategies are required in constructing better fracture prevention care for the elderly. The National Osteoporosis Foundation Guidelines for Pharmacologic Treatment of Osteoporosis recommends pharmacological treatments to postmenopausal women and men aged ≥ 50 years with a history of hip/vertebral fracture, presenting with BMD T-score between -1.0 and -2.5 at the femoral neck/spine or those with a T-score ≤ -2.5 at the femoral neck/spine.¹¹ These populations have a 10-year risk of hip fracture $\geq 3\%$ or 10-year risk of major osteoporosis-related fracture $\geq 20\%$ by Fracture Risk Assessment Tool (FRAX) calculation.¹² Anti-osteoporotic therapy has been demonstrated to reduce mortality in patients with osteoporosis who have been reported to be at risk of high mortality.^{13–15} Given the higher chance of refracture among the fracture population, post-fracture anti-osteoporosis treatment is important in reducing the burden of fragility fracture.

Denosumab is a human recombinant monoclonal antibody that prevents the binding of receptor activator of nuclear factor kappa-B (RANK) ligand (RANKL) to RANK on osteoclasts, thereby suppressing bone resorption.^{16,17} It is one of the most commonly prescribed antiresorptive drugs in clinical practice for the management of osteoporosis in postmenopausal women.¹⁸ Denosumab is reported to increase BMD, inhibit high bone turnover and reduce fracture risk in postmenopausal women with osteoporosis.^{19,20} A potential rise in the risk of multiple vertebral fractures follows discontinuation of denosumab.²¹ Several reviews on the effects of denosumab on BMD have been published.^{22–24} In this article, the effects of denosumab alone or in comparison with other anti-resorptive drugs in fracture/refracture risk reduction among the elderly are reviewed. We also addressed the mortality rate and safety of denosumab use in patients with osteoporosis.

Overview of the Human Studies

A total of 22 original research articles reporting the anti-fracture effects of denosumab from human retrospective cohort and clinical trials were included in this review. Human studies that did not report the fracture incidence or risk are not included. There are two retrospective cohort studies utilizing national data,^{25,26} seven articles from Fracture REduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) clinical trial and FREEDOM extension,^{27–33} nine articles on post hoc analysis of FREEDOM data^{31,39} (wherein 2 articles reporting

both post hoc analysis and FREEDOM extension),^{32,33} one article from Austrian Breast Cancer Study Group study (ABCSG-18),⁴⁰ one article from Denosumab fracture Intervention RandomizEd placebo Controlled Trial (DIRECT),⁴¹ two articles from FRActure study in postmenopausal women with osteoporosis study (FRAME)^{42,43} and two articles from a randomized controlled trial (RCT) by Saag et al.^{44,45} The denosumab was administered at 60 mg subcutaneously once in every 6 months in these clinical trials. However, the treatment period, dose and compliance of denosumab are not known for retrospective cohort studies.^{25,26}

Two retrospective cohort studies compared the anti-fracture effects of denosumab with bisphosphonates.^{25,26} Behavona et al analyzed the national data (98% coverage; $n=47,139$) in Austria among patients aged ≥ 50 years, who experienced a hip fracture between January 2012 and December 2016, and then either left untreated or treated with denosumab or bisphosphonates (oral or intravenous).²⁵ They were tracked up to 60 months for any incidence of subsequent hip fracture and all-cause mortality as study outcomes.²⁵ Pederson et al performed a similar nationwide, population-based, historical cohort study from Danish health registries or database.²⁶ A total of 92,355 subjects aged ≥ 50 years and received the first dispensing of denosumab or alendronate from May 2010 to December 2017 without any antiosteoporosis medication within 1 year were included in the retrospective analysis.²⁶ These subjects were follow-up up to 7.5 years for any hip or other fracture as study outcomes.²⁶ The data were analyzed by treatment condition and then further with subgroup analysis by sex, age, and prior history of hip or any fracture.²⁶

To date, more than 6 completed clinical trials related to denosumab had been reported. FREEDOM trial is an international Phase 3 randomized, placebo-controlled trial designed to investigate the effect of denosumab on fracture risk in postmenopausal women aged 60–90 years with a BMD T-score of less than -2.5 at the lumbar spine or total hip in a 3-year follow-up period.^{28,46,47} It was started in August 2004 and completed in June 2008, and involved 7808 postmenopausal women as either placebo ($N=3902$) or denosumab groups ($N=3906$).^{28,47} Placebo or 60 mg denosumab was administered subcutaneously once every 6 months for 3 years.^{28,47} The new vertebral, non-vertebral or hip fracture incidence were recorded as primary outcomes.^{28,47} A continuation of FREEDOM trial (also known as FREEDOM extension) was conducted, wherein all subjects (both placebo and denosumab groups) who did

not miss more than 1 dose of the investigational product were recruited to receive the denosumab up to an additional 7 years.^{27,29–33} The placebo of FREEDOM trial was noted as “cross-over group” because they received denosumab in the FREEDOM extension while denosumab group continued to receive denosumab up to 10 years and was named the “long-term group”.^{27,29–33}

ABCSG-18 study is a prospective, double-blind, placebo-controlled, multicentre phase 3 trial on 3420 postmenopausal women with hormone receptor-positive breast cancer and underwent aromatase inhibitor as treatment.⁴⁰ All subjects were randomly assigned to receive either denosumab (N=1274) or placebo (N=1188) up to 7 years with a median time of study of 38 months.⁴⁰

DIRECT was a randomized, double-blind, placebo-controlled trial that evaluates the anti-fracture effects of denosumab on both Japanese postmenopausal women and men with osteoporosis.⁴¹ A total of 1034 Japanese postmenopausal women and men, aged ≥ 50 years, with BMD T-score < -1.7 (lumbar spine) or < -1.6 (total hip) with 1–4 prevalent vertebral fractures were randomly assigned in a 2:2:1 ratio to receive either placebo (N=416), denosumab (N=414), or 35 mg oral alendronate weekly (N=204) for 24 months.⁴¹

FRAME trial is an international, randomized, double-blind, placebo-controlled, phase 3 trial on postmenopausal

women with osteoporosis.^{42,43} A total of 7180 postmenopausal women, aged 55–90 years and with a total hip or femoral neck BMD T-score of -3.5 to -2.5 were randomly assigned to receive either placebo or romosozumab (at a dose of 210 mg) monthly for the first 12 months; and subsequently subcutaneous administration of denosumab up to 24 months.^{42,43} Miyauchi et al performed a subgroup analysis on the Japanese subjects (with romosozumab (N=247) and placebo (N=245)).⁴³

Lastly, Saag et al had conducted a phase 3, international, randomized, double-blind, double-dummy, active-controlled, non-inferiority clinical trial on patients with glucocorticoid-induced osteoporosis (N=590) with the lumbar spine, total hip or femoral neck BMD T-score ≤ -2.0 or ≤ -1.0 with fracture history or past osteoporosis-related fracture history.^{44,45} Subjects receiving glucocorticoid therapy for less than 3 months before screening was grouped as “glucocorticoid-initiating group” (n=253) while those with more than 3 months therapy were grouped as “glucocorticoid-continuing group” (n=438).^{44,45} All subjects were randomly assigned either subcutaneous denosumab and oral placebo daily for 24 months, or oral risedronate 5 mg daily with subcutaneous placebo every 6 months for 24 months.^{44,45}

Figure 1 provides an overview of the human retrospective cohorts and clinical trials included in this review.

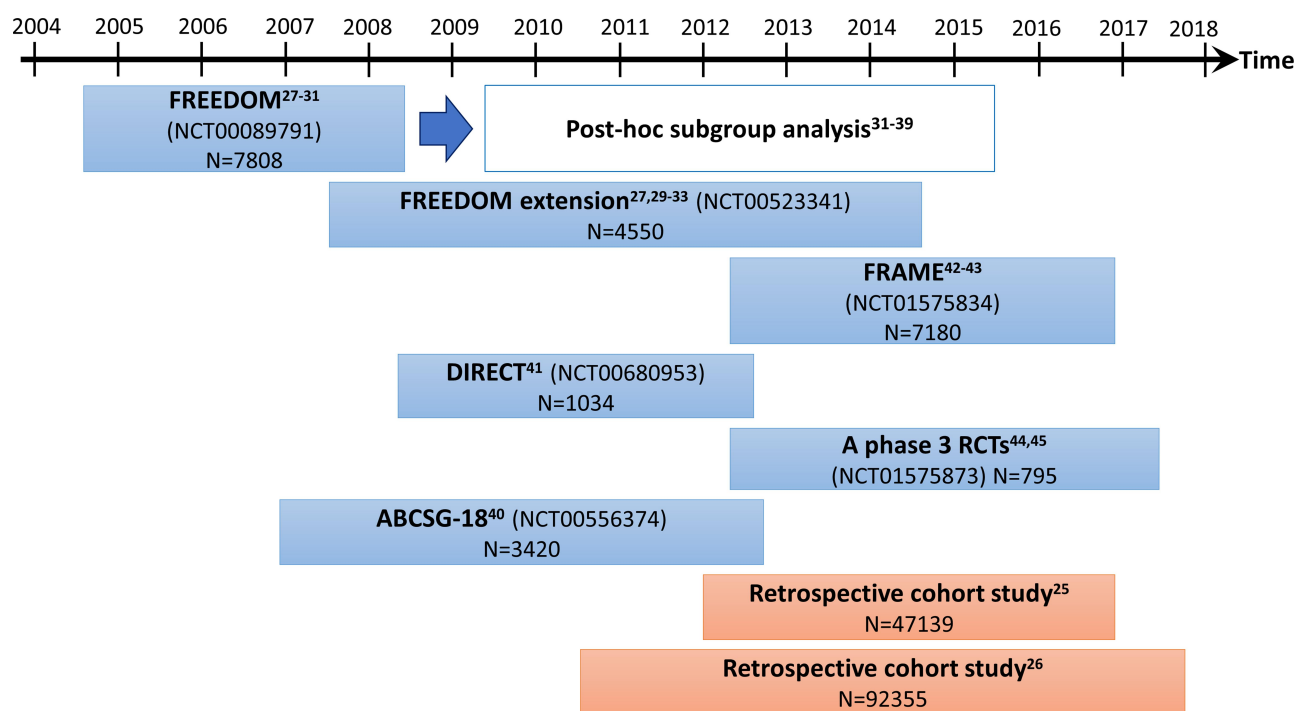


Figure 1 An overview of the human retrospective cohorts and clinical trials included in this review.

The Effect of Denosumab on Vertebral Fracture Risk Reduction

In the FREEDOM trial, 36-month denosumab treatment significantly reduced the risk of new vertebral fracture, new clinical vertebral fracture, multiple new vertebral fractures, new or worsening vertebral fracture, clinical osteoporotic fractures (vertebral and non-vertebral fractures) and primary or secondary fragility fracture (new vertebral and low-trauma non-vertebral fracture).^{28,30,31,33–38,48} Parallely, in ABCSG-18 trial, 36-month denosumab treatment also significantly reduced the new vertebral fracture, new or worsening vertebral fracture incidences, as well as the first clinical fracture among breast cancer patients treated with an aromatase inhibitor.⁴⁰ Similar fracture risk reduction was also reported as early as 12-month denosumab treatment during FREEDOM and DIRECT study.^{28,30,34,35,41} Denosumab was also as effective as risedronate in reducing the fracture incidences, including any osteoporosis-related fracture and new or worsening vertebral fractures upon 24-month treatment.⁴⁵ The efficacy of denosumab and risedronate were similar regardless of sex and menopause status in women.^{44,45}

Additionally, denosumab also reduced new vertebral fracture incidence during the 2–7 years of FREEDOM extension.^{27,30,31} New vertebral fracture incidence was initially high in the placebo group during the FREEDOM study,^{30,31} but decreased sharply during the first 2 years of denosumab treatment³⁰ and remained low throughout the 7 years of FREEDOM extension.²⁷ The trend of fracture risk reduction in the cross-over group was similar to the FREEDOM denosumab group in the first 2 years of denosumab treatment.³⁰ Additionally, the cumulative new vertebral fracture incidence of the long-term group was also significantly reduced in both FREEDOM study and the 7-year FREEDOM extension.²⁷ Moreover, denosumab reduced the exposure-adjusted subsequent osteoporotic fracture rate during FREEDOM trial as well as on all subjects receiving denosumab during the 7-year FREEDOM extension.³³

FREEDOM post hoc analyses demonstrated a greater anti-fracture effect of denosumab in certain subgroups.^{33–35,37,41} Denosumab significantly reduced the new vertebral fracture incidences in the high-risk subgroup with prevalent vertebral fracture and/or vertebral deformity or those with baseline femoral neck BMD T-score of ≤ -2.5 or those with all above risk factors after 24 and 36 months.³⁵ McCloskey et al also reported that the efficacy of denosumab was better on patients

with moderate to high fracture risk and low body mass index.³⁷ Additionally, 24-month denosumab reduced the risk of new or worsening vertebral fracture among Japanese postmenopausal women but not men during the DIRECT study.⁴¹ Recently, Kendler et al also reported a higher fracture risk reduction among subjects with a history of osteoporotic fracture with denosumab treatment.³³

On the other hand, McClung et al reported the efficacy of denosumab in new vertebral fracture risk reduction was independent of age, race, region, body mass index, estimated creatinine clearance, femoral neck BMD, prevalent vertebral fracture, prior non-vertebral fracture and prior use of osteoporosis medications upon a post-hoc analysis on FREEDOM data.³⁸ A similar finding by Palacios et al also reported that the anti-fracture effects of denosumab were independent of age, prior fragility fracture history, fracture site, previous osteoporotic treatment history as well as those presented with both risk factors of age and prior fragility fracture.⁴⁸ Similarly, denosumab reduced the osteoporotic fracture regardless of age, femoral neck BMD value, prior fracture, parental history of hip fracture, secondary causes of osteoporosis, smoking or alcohol intake in another FREEDOM post-hoc analysis.³⁷ Similarly, prevalent vertebral fracture, femoral neck BMD and the functionality of the kidney also did not affect the efficacy of denosumab on fracture risk reduction.^{35,36,40}

The Effect of Denosumab on Hip Fracture Risk Reduction

Two retrospective cohort studies were conducted to evaluate the effects of denosumab in reducing bone fracture.^{25,26} Behavona et al reported no significant difference in subsequent hip fracture risk between denosumab and bisphosphonate groups.²⁵ Surprisingly, patients treated with bisphosphonates and denosumab experienced a higher risk and cumulative incidence of subsequent hip fracture compared to patients without antiresorptive treatment.²⁵ The increase in subsequent hip fracture risk was more prominent among women receiving denosumab.²⁵ The increase of subsequent hip fracture risk with denosumab treatment might be due to a short follow-up time or confounders, such as alcohol consumption, physical activity, nutrition and/or medication adherence.²⁵ Sample size for the denosumab group was relatively small (N=555) as compared with untreated patients (N=42,795).²⁵ A recent retrospective cohort study by Pederson et al identified that hip fracture risk was similar between patients treated with denosumab and alendronate

within 3 years of follow-up, regardless of sex, age, previous history of hip fracture or any fracture.²⁶ Subgroup analysis revealed a marginally lower risk among women, subjects <80 years old, those with or without a history of any fracture and those without previous hip fracture compared to alendronate.²⁶

In FREEDOM study, 36-month denosumab treatment significantly reduced the risk of hip fractures compared to placebo.^{28,30,35,36} Prolonged (>3 years) denosumab treatment reduced the hip fracture incidence during the first 3 years of FREEDOM trial, then further reduced and maintained it throughout the 7 years of FREEDOM extension.²⁹⁻³¹ A similar trend was detected in the cross-over group, where the hip fracture incidence was significantly reduced, reaching a level comparable to the long-term group at the end of FREEDOM extension.^{27,29-31} Boonen et al reported that denosumab could significantly reduce the risk of hip fractures in the entire FREEDOM population as well as high-risk subgroups, for example, subjects aged ≥ 75 years; baseline femoral neck BMD T-score of ≤ -2.5 or those with both risk factors.³⁵ There was no significant difference in hip fracture risk reduction between denosumab and placebo for low-risk subgroups due to the low baseline hip fracture risk.³⁵ Parallely, in the FREEDOM post-hoc subgroup analysis, denosumab did not reduce hip fractures after adjusting for age and major osteoporotic fracture probability calculated by FRAX.³⁷

The Effect of Denosumab on Non-Vertebral Fracture Risk Reduction

In FREEDOM study, 36-month denosumab treatment significantly reduced the risk of non-vertebral fractures compared to placebo.^{28,30,35,36,38} The anti-fracture effects of denosumab in the non-vertebral or other minor fractures are heterogeneous, especially with shorter treatment time. Saag et al reported that the efficacy of denosumab in reducing low-trauma non-vertebral fractures was similar to risedronate during a 24-month treatment frame.^{44,45} However, marginal non-vertebral fracture risk reduction was reported after 12- and 24-month denosumab treatment.^{34,41} Additionally, Nakamura et al also reported that 24-month denosumab increased the risk of non-major non-vertebral fracture to 2.5% as compared to 0.4% among placebo.⁴¹ Thus, the efficacy of denosumab in reducing non-vertebral fracture risk needs to be investigated further.

Prolonged (>3 years) denosumab treatment resulted in a similar or even better fracture risk reduction compared with shorter treatment. Denosumab reduced the non-vertebral fracture incidence during the first 3 years of FREEDOM trial, then further reduced and maintained it throughout the 7 years of FREEDOM extension.^{27,29-31} A similar trend was detected in the cross-over group, where the non-vertebral fracture incidence was significantly reduced, reaching a comparable level as the long-term group at the end of FREEDOM extension.^{27,29-31} The non-vertebral fracture incidence was significantly higher among FREEDOM placebo and the twin-estimated placebo in FREEDOM extension.³⁰ It can be concluded that the anti-fracture effect of denosumab is only significant after ≥ 3 years of treatment.

In the FREEDOM post-hoc subgroup analysis, denosumab significantly reduced the clinical osteoporotic fractures after adjusting for age and FRAX major osteoporotic fracture probability.³⁷ Denosumab only significantly reduced the non-vertebral fracture risk in those subgroups with BMI < 25 kg/m², femoral neck BMD T-score ≤ -2.5 or without a prevalent vertebral fracture.³⁸ Additionally, the efficacy of denosumab on non-vertebral fracture was independent of age groups, kidney function, total hip BMD, and prior history of non-vertebral fracture.^{34,36,38} Subgroup analysis revealed that denosumab-induced non-vertebral fracture risk reduction was more prominent among subjects with the lower hip (T-score between -1.0 and -2.5) or femoral neck BMD (T-score ≤ -2.5) during FREEDOM extension.²⁹ In other words, the risk reduction effects of denosumab in a specific subgroup may be marginal and only become prominent upon a longer treatment time. Additionally, the selection of inclusion and exclusion criteria and subgrouping definition may also affect the outcome in subgroup analysis.

The Effect of Denosumab on Wrist and Other Fracture Risk Reduction

The effects of denosumab on wrist and other fractures, including forearm and humerus fractures, were also reported. However, the effects might not be as significant as major fractures.^{32,39} Denosumab significantly reduced the wrist fracture incidence for FREEDOM subgroup with a femoral neck T-score ≤ -2.5 , but not for the entire FREEDOM population.³⁹ Bilezikian et al also reported the beneficial effects of denosumab on upper limb fractures during the 7-year FREEDOM extension.³² Denosumab

significantly reduced the humerus but not wrist and forearm fracture rate among the extension group during the 1st–3rd year of FREEDOM extension.³² The overall fracture rate for upper limbs, including wrist, forearm and humerus fractures, was significantly lower in the extension group during the 4th–7th year of FREEDOM extension.³² Parallel with vertebral and non-vertebral fracture, this observation also suggested that a longer denosumab treatment is necessary to optimize its anti-fracture effects for the upper limbs.

Figure 2 summarizes the effects of denosumab on vertebral, non-vertebral, hip, wrist and other fractures risk reduction.

Comparison of the Fracture Risk Reduction Between Denosumab and Other Anti-Osteoporotic Drugs

The retrospective cohort study by Pedersen et al compared the risk of hip and any fracture between patients treated with denosumab and alendronate.²⁶ The hazard ratios of hip fractures for both denosumab and alendronate were similar regardless of sex, age, or fracture history.²⁶ On the other hand, denosumab was more potent than risedronate in improving BMD as evidenced in an RCT study.^{44,45} Denosumab, as compared to risedronate, significantly increased the percentage change of BMDs at the lumbar

spine, total hip, femoral neck and 1/3 radius among those glucocorticoid-treated subjects.^{44,45} There was an early downregulation of serum BTM levels prior to the increase of BMDs upon denosumab treatment.^{44,45}

On the other hand, the anti-osteoporotic effects of combined denosumab and romosozumab among postmenopausal women were studied in the FRAME trial.^{42,43} Subjects with 1 year of romosozumab followed by another year of denosumab showed a similar incidence of non-vertebral and clinical fracture.⁴² With the continuation of an extra 1 year of denosumab treatment, no significant reduction in new vertebral, clinical, non-vertebral, major non-vertebral, major osteoporotic, clinical new or worsening vertebral and hip fractures was observed compared to subjects with the first year of placebo and subsequent 2 years of denosumab.⁴³ Denosumab did increase the BMDs in both groups. However, the pre-treatment of romosozumab significantly increased patients' BMD from the baseline values.^{42,43} The anti-fracture effects of romosozumab-denosumab combination need to be further confirmed via a larger sample size and/or longer treatment time.

Teriparatide is the first approved anabolic agent that stimulates osteoblastic bone formation.^{49,50} The anti-osteoporotic effects of teriparatide, denosumab and other anti-osteoporotic agents have been examined in systematic review and meta-analysis recently.⁵¹ Both teriparatide

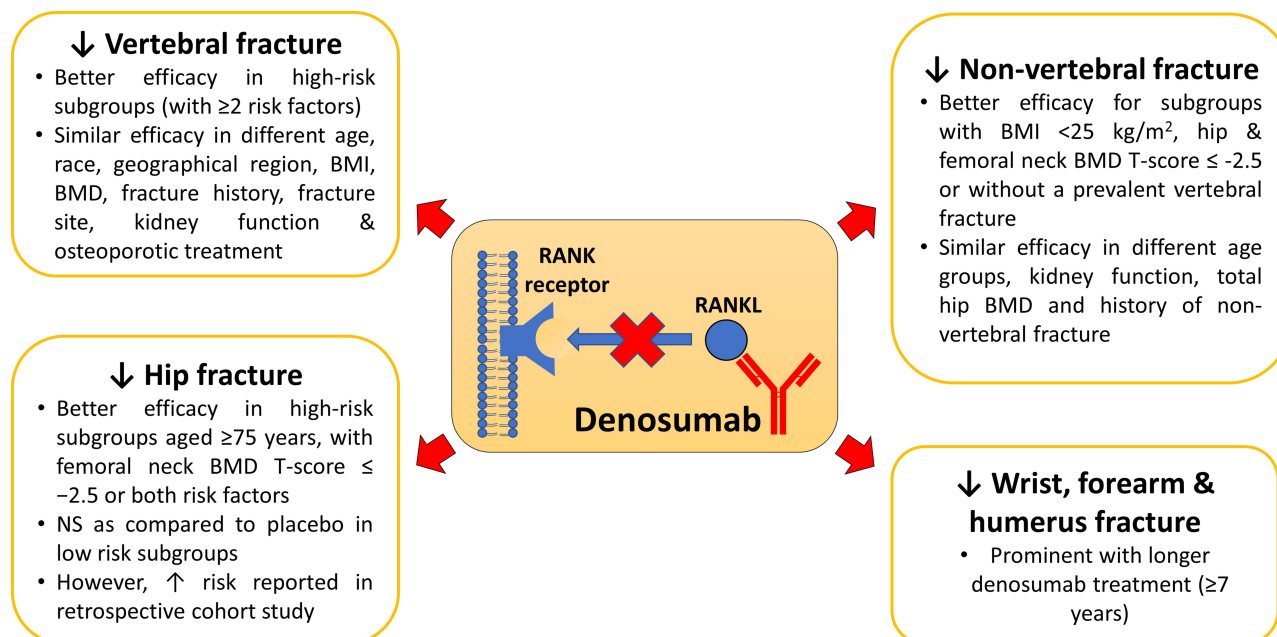


Figure 2 The anti-fracture effects of denosumab in vertebral, non-vertebral, hip, wrist and other fractures.

Notes: \uparrow Increase; \downarrow Decrease.

Abbreviations: BMI, body mass index; BMD, bone mass density; NS, non-significant; RANKL, receptor activator of nuclear factor kappa-B ligand.

(daily dose of 20–40 µg) and denosumab were effective in reducing vertebral fracture risk by 86% and 68%, respectively.⁵¹ However, the between-groups comparison was not performed by the authors. In the Denosumab and Teriparatide Administration randomized trial (DATA), 12-month denosumab was superior to teriparatide based on the increment of BMDs at femoral neck, total hip and distal 1/3 of radial shaft.⁵² In the DATA extension study, 24-month teriparatide was as effective as denosumab in increasing the BMDs at the lumbar spine, femoral neck and total hip.⁵³ Denosumab, but not teriparatide, significantly increased the BMD at the 1/3 distal radius.⁵³

Short-term teriparatide treatment is preferable given its potential carcinogenic effect, based on the osteosarcoma induction in rats upon long-term exposure (2-year).^{54,55} A shorter (3 to 6 months) but cyclic approach of teriparatide could exert a similar or slightly weaker anti-osteoporotic effect compared to standard daily teriparatide treatment.⁵⁶ Moreover, the cyclic teriparatide treatment with three cycles of teriparatide (6 months) to denosumab (6 months) was similar to standard sequential teriparatide (18 months) to denosumab (18 months) treatment in increasing the BMDs at spine, total femur, femoral neck and 1/3 radius.⁵⁷ On the other hand, in DATA-Switch study, co-treatment of teriparatide and denosumab for 24 months, followed by 24-month denosumab alone was more potent in increasing the BMDs at total hip, femoral neck and radius bone (but not lumbar spine) than sequential treatments with teriparatide (24 months) to denosumab (24 months) or vice versa.^{58,59} Similar findings were obtained in the DATA and DATA extension study, whereby the co-treatment of teriparatide and denosumab induced a greater increase in BMDs.^{52,53}

A summary of the anti-fracture effects of denosumab is presented in [Table 1](#).

Discontinuation of Denosumab and Fracture Risk

The effect of denosumab discontinuation on fracture risk has been reviewed extensively.^{21,60,61} Denosumab discontinuation is closely associated with a rebound effect, indicated increased BTM levels and the parallel loss of gained BMD within 6–24 months of discontinuation, as reported in several case reports, observational study, RCTs and post-hoc analysis of FREEDOM data.^{62–67} Additionally, denosumab discontinuation also resulted in a higher risk of rebound-associated vertebral fracture, including multiple vertebral fractures.^{68–72}

The simultaneous reactivation of all dormant osteoclasts at once after denosumab discontinuation, which subsequently leads to excessive bone resorption, is suggested to be the mechanism of rebound effect.⁷³ As evidence, an early 5- to 7-fold increase of CTX and PINP levels after the 3-month discontinuation of denosumab was observed. This effect was accompanied by an increase in RANKL level and a gradual decrease in Dickkopf-1 and sclerostin level.⁷⁴ A recent histomorphological analysis on bone biopsies from fracture patients also confirmed that denosumab discontinuation caused a higher bone turnover activity and bone structures and hardness reduction, which may explain the rebound-associated fracture.⁷⁵ Moreover, there is a downregulation of miR-503 and miR-222-2 (miRNAs that downregulate osteoclastogenesis) upon denosumab discontinuation, which leads to the subsequent upregulation of RANK and cathepsin K mRNAs.⁷³ The optimum treatment after discontinuation of denosumab is not yet established. The re-initiation of denosumab was reported to increase the BMDs again, but a very recent case report from Niimi et al showed that re-initiation of denosumab did not eliminate the risk of rebound-associated vertebral fractures.^{70,76} A pre-treatment or follow-up course of bisphosphonates upon denosumab discontinuation was found to be protective by maintaining BMDs and CTX levels, possibly via the reduction of the dormant osteoclasts.^{74,77–80} Further investigation is required to elucidate the underlying mechanisms of denosumab discontinuation and establish a proper strategy to overcome fractures associated with it.

Mortality Rate and Safety of Denosumab in Patients

Subcutaneous administration of denosumab (60 mg every 6 months) is safe for human as the mortality rate is reduced or maintained at the same level as the placebo.^{25,27,35} A retrospective cohort study by Behanova et al reported that denosumab treatment (as well as bisphosphonate) significantly reduced the risk of mortality as compared to untreated patients.²⁵ Subgroup analysis also identified that the mortality-reducing effect of denosumab was more prominent in men than women.²⁵ Additionally, denosumab also significantly reduced the mortality rate among high-risk subjects based on prevalent vertebral fracture status with or without a low femoral neck BMD.³⁵ Comparing with risedronate, there was a 1% increase in mortality rate upon denosumab treatment.^{44,45} However, statistical analysis was not performed.

Table 1 The Anti-Fracture Effects of Denosumab in the Retrospective Cohort and Clinical Trials

No.	Reference	Study Design	Subjects	Intervention Description	Outcomes
1	Cummings et al, 2009 ²⁸	Randomised controlled trial (FREEDOM; ClinicalTrials.gov: NCT00089791)	A total of 7808 postmenopausal women aged 60–90 years with a T score < -2.5 at the lumbar spine or total hip.	Subjects received subcutaneous injections of either 60 mg denosumab or placebo every 6 months for 36 months. All women received daily supplements containing calcium (≥ 1 g) and vitamin D (≥ 400 IU).	<ul style="list-style-type: none"> ↓ risk of new vertebral fracture by 68% after 36 months [relative risk (RR)= 0.32; 95% confidence interval (CI) 0.26–0.41; $p < 0.001$]. Similar trends of new vertebral fracture reduction were identified for 0–12 [RR= 0.39], 12–24 [RR= 0.22] and 24–36 months intervals [RR= 0.35] (all $p < 0.001$). ↓ risk of secondary non-vertebral fracture by 19% [hazard ratio (HR)= 0.80; 95% CI 0.67–0.95; $p < 0.05$], risk of hip fracture by 41% [HR= 0.60; 95% CI 0.37–0.97; $p < 0.05$], risk of new clinical vertebral fracture by 69% [HR= 0.31; 95% CI 0.20–0.47; $p < 0.001$] and risk of multiple new vertebral fractures by 63% after 36 months [HR= 0.39; 95% CI 0.24–0.63; $p < 0.001$]. ↓ incidence of falls that were not associated with a fracture to 4.5% as compared with 5.7% in the placebo group after 36 months ($p < 0.05$). No significant difference between subjects who received denosumab and placebo in the total incidence of adverse events, serious adverse events, or discontinuation of study treatment because of adverse events ($p > 0.05$).
2	Papapoulos et al, 2012 ³⁰	FREEDOM and FREEDOM extension study (ClinicalTrials.gov: NCT00523341)	A total of 7808 subjects from FREEDOM trial and 4550 subjects from both placebo (N=2207) and denosumab groups (N=2343) who completed the 3-year FREEDOM trial and did not discontinue investigational product or miss > 1 dose in the first 2 years of FREEDOM extension study.	Similar intervention as Cummings et al 2009. During the FREEDOM extension, all subjects (denosumab and placebo) were administered 60 mg denosumab subcutaneously every 6 months for the first 2 years with daily calcium and vitamin D supplementation. Cross-over group: all subjects from placebo of FREEDOM study who received the denosumab in the extension. Long-term group: Subjects who continued denosumab for 2 years in addition to the 3 years initial treatment (total 5 years of treatment).	<ul style="list-style-type: none"> ↓ risk of new vertebral and non-vertebral fractures for each year of denosumab in FREEDOM trial compared with placebo. New vertebral fracture incidence remained low at 1.4% for "long-term group" during the FREEDOM extension and ↓ sharply to 0.9% for "cross-over group". ↓ non-vertebral fracture incidence reaching 1.4% and 1.1% for "long-term group" at 4th and 5th year of treatment. ↓ non-vertebral fracture incidence, reaching 2.4% and 1.7% during 1st and 2nd year of FREEDOM extension, respectively, with trends similar to conventional denosumab group in original FREEDOM trial. Adverse events did not increase with 5 years of denosumab administration.

3	Ferrari et al, 2015 ²⁹	FREEDOM and FREEDOM extension study (ClinicalTrials.gov: NCT00523341)	A total of 4074 subjects (N=2343 denosumab; N=1731 placebo) who completed the 3-year FREEDOM trial and did not discontinue investigational product or miss > 1 dose for the first 4 years in the FREEDOM extension.	Similar intervention as Papapoulos et al 2012 but up to 3 years. Cross-over group: all subjects from placebo of FREEDOM study who received the denosumab in the extension. Long-term group: Subjects who continued denosumab for 4 years in addition to the 3 years initial treatment (total 7 years of treatment).	<ul style="list-style-type: none"> ● Low non-vertebral fracture incidences in the first 4 years of denosumab extension for both long-term group (1.5%, 1.2%, 1.8% and 1.6%, respectively) and cross-over group (2.3%, 2.1%, 2.7% and 1.2%, respectively). ● Non-vertebral fracture rate per 100 participant-years among all subjects in FREEDOM extension was 2.15% in the first 3 years of extension and then ↓ by 36% in the 4th year of extension [RR=0.64; 95% CI 0.48–0.85; p< 0.01]. ● Non-vertebral fracture rate among cross-over group was 2.37% in the first 3 years of extension and then ↓ by 49% in the 4th year of extension [RR= 0.51; 95% CI 0.32–0.82; p<0.01]. ● Non-vertebral fracture rate was similar between the first 3 years of denosumab (FREEDOM) and 1st year of extension in the long-term group (p=0.127). The fracture rate ↓ by 21% in the long-term group [RR=0.79; 95% CI 0.62–1.00, p<0.05]. ● Non-vertebral fracture rate reductions in 4th year of extension were most prominent for subjects with hip BMD between -1.0 and -2.5 [RR=0.47; 95% CI 0.30–0.73; p-value N/A] and femoral neck BMD T-score of ≤-2.5 [RR=0.37; 95% CI 0.18–0.77; p< 0.01]. The reduction was not significant between the first 3 years and 4th year of extension (p>0.05).
---	-----------------------------------	---	---	---	---

(Continued)

Table 1 (Continued).

No.	Reference	Study Design	Subjects	Intervention Description	Outcomes
4	Papapoulos et al, 2015 ³¹	FREEDOM and FREEDOM extension study (ClinicalTrials.gov: NCT00523341)	A total of 7808 subjects from FREEDOM trial and 3004 subjects from both placebo (N=1462) and denosumab groups (N=1542) who completed the 3-year FREEDOM trial and did not discontinue investigational product or miss >1 dose in the first 5 years of FREEDOM extension.	Similar intervention as Cummings et al 2009, and Papapoulos et al 2012 (up to 5 years). Cross-over group: all subjects from placebo of FREEDOM study who received the denosumab in the extension. Long-term group: Subjects who continued denosumab for 5 years in addition to the 3 years initial treatment (total 8 years of treatment).	<ul style="list-style-type: none"> ● Low incidence of new vertebral fractures in the "long-term group" at 1.5%, 1.3% and 1.3% for 4/5th, 6th and 7/8th year of treatment. ● ↓ incidence of new vertebral fractures in the "cross-over group" compared to placebo period in FREEDOM, at 0.9% (1/2nd year), 1.6% (3rd year of extension) and 1.8% (4/5th year of extension). ● ↓ incidence of non-vertebral fractures in "long-term group" at 1.5% (4th year), 1.2% (5th year), 1.8% (6th year), 1.6% (7th year) and 0.7% (8th year of treatment). ● ↓ incidence of non-vertebral fractures in "cross-over group" compared to placebo in FREEDOM, at 0.9% (1/2nd years), 1.6% (3rd years of extension) and 1.8% (4/5th years of extension). ● The cumulative incidence of hip fractures for 1st to 5th year of the extension was 0.7% and the annualized incidence of hip fractures with up to 8 years of denosumab treatment was 0.2% for "long-term group". ● The cumulative incidence of hip fractures for 1st to 5th year of the extension was 1.1% for "cross-over group". ● The incidence of adverse and serious adverse events did not increase over time regardless of the length of denosumab treatment.

5	Bone et al, 2017 ²⁷	FREEDOM and FREEDOM extension study (ClinicalTrials.gov: NCT00523341)	A total of 7808 subjects from FREEDOM trial and 2626 subjects from both placebo (N=1283) and denosumab groups (N=1343) who completed the 3-year FREEDOM trial and did not discontinue investigational product or miss > 1 dose for 7 years in the FREEDOM extension.	Similar intervention as Cummings et al 2009, and Papapoulos et al 2012 (up to 7 years). Cross-over group: all subjects from placebo of FREEDOM study who received the denosumab in the extension. Long-term group: Subjects who continued denosumab for 7 years in addition to the 3 years initial treatment (total 10 years of treatment).	<ul style="list-style-type: none"> • The new vertebral fracture incidences in the long-term group were maintained at 0.86%, 0.70% and 1.08% during FREEDOM trial and then 1.47%, 1.16%, 1.36% and 1.28% in the 4/5th, 6th, 7/8th and 9/10th year of denosumab treatment. • The non-vertebral fracture incidences in long-term group were maintained at 2.59%, 2.09% and 2.15% during FREEDOM trial and then ↓ to 1.49%, 1.23%, 1.77%, 1.55%, 0.84%, 1.05% and 1.91% for 4–10 years of denosumab. • The hip fracture incidences in the long-term group were consistently maintained at 0.29%, 0.08% and 0.32% in FREEDOM trial and then 0.22%, 0.05%, 0.15%, 0.05%, 0.18%, 0.00% and 0.42% during 4–10 years of denosumab. • The new vertebral fracture incidences in cross-over group remained low at 0.90%, 1.47%, 1.86% and 1.58% during the 1/2nd, 3rd, 4/5th and 6/7th year of denosumab extension treatment. • The non-vertebral fracture incidences in cross-over group were maintained at 2.55%, 2.00%, 2.55%, 1.18%, 1.77%, 1.53% and 1.72% for the 1–7 years of denosumab extension, respectively. • The hip fracture incidences in cross-over group were maintained at 0.61% in the first year of denosumab treatment and ↓ to 0.14%, 0.16%, 0.06%, 0.13%, 0.14% and 0.07% during 2–7 years of denosumab, respectively. • The cumulative new vertebral fracture incidence in the long-term group was ↓ by 68% to 2.3% (placebo 7.2%) in FREEDOM trial, but ↑ back to baseline at 7.0% in the FREEDOM 7-year extension with a much higher estimated virtual twin-placebo (11.5%). • The cumulative non-vertebral fracture incidence in the long-term group ↓ by 19% to 6.5% (placebo 8.0%) in FREEDOM trial and then ↑ 9.3% during the FREEDOM 7-year extension with a relatively higher estimated virtual twin-placebo (14.5%). • The estimated relative risk for new vertebral fracture in the long-term group was 0.62 (95% CI 0.47–0.80), while the non-vertebral fracture was 0.54 (95% CI 0.43–0.68) with the unknown <i>p</i>-value. • All and serious adverse events including infections, malignancy, eczema, hypocalcaemia, pancreatitis, cellulitis and fatality remained stable over the time for both placebo (FREEDOM) and denosumab-treated group (long-term and cross-over group).
---	--------------------------------	---	--	---	---

(Continued)

Table 1 (Continued).

No.	Reference	Study Design	Subjects	Intervention Description	Outcomes
6	Kendler et al, 2019 ³³	Post-hoc analysis of FREEDOM and FREEDOM extension study (ClinicalTrials.gov: NCT00523341)	A total of 710 FREEDOM subjects and 794 subjects from FREEDOM and FREEDOM extension respectively who had an osteoporotic fracture (new vertebral or non-vertebral fracture) and then continued post-fracture treatment at least ≥ 2 doses of placebo or denosumab.	Similar intervention as Cummings et al 2009, and Papapoulos et al 2012 (up to 7 years). Cross-over group: all subjects from placebo of FREEDOM study who received the denosumab in the extension. Long-term group: Subjects who continued denosumab for 7 years in addition to the 3 years initial treatment (total 10 years of treatment). Combined denosumab group: Denosumab users in long-term group and/or cross-over group.	<ul style="list-style-type: none"> • \downarrow multiple new vertebral fracture by 62.5% as compared with placebo (1.6%) [RR= 0.39, 95% CI 0.24–0.63]. • \downarrow exposure-adjusted subsequent osteoporotic fracture rate, per 100 subject-years (vertebral or non-vertebral fracture) in combined denosumab group (but not FREEDOM denosumab group) by 43% to 5.8% compared with placebo (10.1%) from FREEDOM [HR= 0.59; 95% CI 0.43–0.81; $p < 0.01$] • \downarrow exposure-adjusted subsequent osteoporotic fracture rate by 40% to 10.4 for denosumab FREEDOM [HR= 0.54; 95% CI: 0.29–0.99; $p < 0.05$] and by 55% to 7.8 in combined denosumab group compared with placebo (17.4%) [HR= 0.41; 95% CI: 0.26–0.65; $p < 0.0001$].
7	Bilezikian et al, 2019 ³²	Post hoc analysis of FREEDOM and FREEDOM extension study (ClinicalTrials.gov: NCT00523341)	A total of 2207 subjects from FREEDOM extension study who had an osteoporotic fracture (new vertebral or non-vertebral fracture) and then continued post-fracture treatment at least ≥ 2 doses of placebo or denosumab. A total of 441 subjects were identified in a BMD sub-study with 209 placebo and 232 denosumab.	Similar intervention as Cummings et al 2009, and Papapoulos et al 2012 (up to 7 years). Cross-over group: all subjects from placebo of FREEDOM study who received the denosumab in the extension. Long-term group: Subjects who continued denosumab for 7 years in addition to the 3 years initial treatment (total 10 years of treatment). Extension group: Cross-over and long-term groups.	<ul style="list-style-type: none"> • A 7-year denosumab significantly decreased the overall rate of entire upper limb fractures in extension group during 4th-7th year [48% reduction; RR= 0.52; 95% CI 0.37–0.72; $p < 0.0001$], including the wrist [43% reduction; RR= 0.57; 95% CI 0.38–0.86; $p = 0.0077$], forearm [43% reduction; RR= 0.57; 95% CI 0.39–0.84; $p = 0.0042$] and humerus [59% reduction; RR= 0.42; 95% CI 0.21–0.83; $p = 0.0129$] as compared with FREEDOM placebo. • The entire upper limb fracture rates including wrist and forearm were similar between FREEDOM placebo and extension group in the 1st-3rd year, except for humerus [54.5% reduction; RR= 0.45; 95% CI: 0.23–0.89; $p < 0.05$].

8	Boonen et al, 2011 ³⁵	Post hoc analysis of FREEDOM data	A total of 7808 postmenopausal women from FREEDOM trial, who were grouped as high- and low-risk subgroups based on fracture prevalent, femoral neck BMD and/or age.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> • ↓ new vertebral fracture incidence at 12, 24 and 36 months by 61% [95% CI 42–74%], 71% [95% CI 61–79%] and 68% [95% CI 59–74%], respectively (all $p < 0.001$). • ↓ incidence of new vertebral fractures in high-risk subgroup based on prevalent vertebral fracture status [55% reduction; absolute risk reduction (ARR) = 9.2%]; baseline femoral neck BMD T-score ≤ -2.5 [69% reduction; ARR = 6.8%]; and high-risk combined subgroup (those with both risk factors) [60% reduction; ARR = 12.3%] (all $p \leq 0.001$) after 36 months. • ↓ incidence of new vertebral fractures in the low-risk subgroup based on absence of prevalent vertebral fracture [71% reduction; ARR = 4.4%]; baseline femoral neck BMD T-score > -2.5 [66% reduction; ARR = 3.7%]; and low-risk combined subgroup (those without one or both of these risk factors) [68% reduction; ARR = 4.5%] (all $p < 0.001$) after 36 months. • ↓ incidence of new vertebral fractures for the high-risk subgroup (based on prevalent vertebral fracture status) by 64% and high-risk combined subgroup by 71% at 24 months (all $p < 0.001$) but not for 12 months ($p > 0.05$). • ↓ incidence of new vertebral fractures for low-risk subgroup and low-risk combined subgroup by 66% and 62% at 12 months and further reduced to 73% and 71% at 24 months, respectively (all $p < 0.001$). • ↓ risk of hip fractures in high-risk subgroups: aged ≥ 75 years [62% reduction; ARR = 1.4%]; baseline femoral neck BMD T-score ≤ -2.5 [47% reduction; ARR = 1.4%] and high-risk combined subgroup (those with both risk factors) [60% reduction; ARR = 2.4%] (all $p < 0.05$). • No significant difference was found in the risk of hip fracture between denosumab and placebo treatment for all low-risk subgroups (all $p > 0.05$). • The anti-fracture efficacy of denosumab against new vertebral fracture and hip fracture was consistent among each low- and high-risk subgroups (with interaction $p > 0.05$). • The frequencies of adverse events were found similar between denosumab and placebo regardless of age (all $p > 0.05$). • Denosumab treatment significantly reduced the fatality rate in high-risk subgroups with prevalent vertebral fracture status, with or without a low femoral neck BMD T-score (all $p < 0.05$).
---	----------------------------------	-----------------------------------	---	--	--

(Continued)

Table 1 (Continued).

No.	Reference	Study Design	Subjects	Intervention Description	Outcomes
9	Jamal et al, 2011 ³⁶	Post-hoc analysis of FREEDOM data	A total of 7808 postmenopausal women from FREEDOM trial, who were grouped based on the modified National Kidney Foundation classification of CKD.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> ↓ incidence of new vertebral fracture [odds ratio (OR)= 0.30; 95% CI 0.23–0.39; $p < 0.001$] and non-vertebral fractures [OR= 0.78; 95% CI 0.66–0.93] after 36 months. ↓ incidence of new vertebral fractures [OR= 0.30; 95% CI 0.23–0.39] in stages 1, 2 and 3 of CKD and ↓ non-vertebral fractures incidence [OR= 0.78; 95% CI 0.66–0.93] in stages 1 and 2 CKD (p values are not provided by authors). The anti-fracture effects of denosumab were not statistically significant among subjects with different kidney function ($p > 0.05$). Denosumab is safe and effective among subjects with stage 1 to stage 4 CKD with similar adverse events.
10	McClung et al 2012 ³⁸	Post-hoc analysis of FREEDOM data	A total of 7808 postmenopausal women from FREEDOM trial, who were grouped into subgroups (age, body mass index, estimated creatinine clearance, region, femoral neck BMD, prevalent vertebral fracture, prior non-vertebral fracture, race and prior use of osteoporosis medications) with their new vertebral fracture, non-vertebral fracture and femoral neck BMD outcomes.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> ↓ incidence of new vertebral fractures by 68% to 2.3% [HR= 0.32; 95% CI 0.26–0.41; $p < 0.001$] and non-vertebral fractures by 19% to 6.5% [HR= 0.80; 95% CI 0.67–0.95; $p = 0.01$] for the entire study population after 36 months. ↓ new vertebral fracture risk regardless of age, BMI, estimated creatinine clearance, region, femoral neck BMD, prevalent vertebral fracture, prior non-vertebral fracture, race and prior use of osteoporosis medications (all $p > 0.05$). ↓ non-vertebral fracture risk regardless of age groups and those with or without prior history of non-vertebral fracture (all $p > 0.05$). ↓ non-vertebral fracture risk in those subgroups with BMI < 25 kg/m² [38% reduction; ARR= 3.4%; 95% CI 1.5–5.3%], with femoral neck BMD T-score ≤ -2.5 [35% reduction; ARR= 4.1%; 95% CI 1.8–6.5%] and in those subgroups without a prevalent vertebral fracture [29% reduction; ARR= 2.1%; 95% CI 0.7–3.4%] (all $p < 0.05$).
11	Austin et al, 2012 ³⁴	Post-hoc analysis of FREEDOM data	A total of 7808 postmenopausal osteoporotic women from FREEDOM study with their total hip BMD and fracture outcomes.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> ↓ new or worsening vertebral fracture risk after 12 months [RR= 0.39; 95% CI 0.26–0.58], 24 months [RR= 0.29; 95% CI 0.21–0.39] and 36 months of treatment [RR= 0.32; 95% CI 0.26–0.41] ↓ non-vertebral fracture risk at 24 months [HR= 0.79; 95% CI 0.64–0.96] and 36 months [HR= 0.80; 95% CI 0.67–0.95] but not 12 months. ↓ new or worsening vertebral fracture (but not nonvertebral fracture) with ↑ total hip BMD in both denosumab and placebo group. The slope of the curves for denosumab was significantly higher than placebo ($p = 0.0003$).

12	McCloskey et al. 2012 ³⁷	Post-hoc analysis of FREEDOM data	Calculation of FRAX based on clinical risk factors and BMD data from the 7808 postmenopausal osteoporotic women in FREEDOM study.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> • ↓ clinical osteoporotic (vertebral and non-vertebral) fractures [RRR=32%; 95% CI 20–42%; $p < 0.001$], but not hip fractures [RRR=36%; 95% CI –2–60%; $p > 0.05$] compared with placebo after adjusted for age and FRAX major osteoporotic fracture probability. • Better efficacy of fracture risk reduction in those with moderate to high fracture risk ($p \leq 0.001$). • Denosumab was equally effective regardless of age, BMD value, prior fracture, parental history of hip fracture, secondary causes of osteoporosis, smoking or alcohol intake (all $p > 0.05$). • A low body mass index (BMI) was associated with greater efficacy of denosumab ($p < 0.05$).
13	Simon et al. 2013 ³⁹	Post-hoc analysis of FREEDOM data	A total of 7808 postmenopausal women from FREEDOM trial with wrist fracture incidence, radius BMD, bone mineral content and strength data.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> • Denosumab significantly reduced wrist fracture incidence for participants with a femoral neck T-score ≤ -2.5 in comparing with placebo [RRR= 40%; ARR= 1.6%; $p < 0.05$]. • Denosumab did not alter the wrist fracture incidence for the entire FREEDOM group [HR= 0.84; RRR= 1.6%; $p = 0.21$] or participants with a femoral neck T-score > -2.5 [RRR= –4%; $p = 0.82$].
14	Palacios et al. 2015 ⁴⁸	Post-hoc analysis of FREEDOM data	A total of 7808 postmenopausal women from FREEDOM trial with the onset of secondary fragility fracture.	Similar intervention as Cummings et al 2009.	<ul style="list-style-type: none"> • ↓ incidence of primary or secondary fragility fracture (new vertebral and low-trauma non-vertebral fracture) in total FREEDOM subjects [RRR=40%; ARR= 5.3%] after 36 months. • Similar anti-fracture effects of denosumab were reported on FREEDOM subpopulations with prior fragility fracture [RRR=39%; ARR= 6.8%] or without prior fragility fracture [RRR=40%; ARR= 4.1%], aged ≥ 75 years [RRR=35%; ARR= 5.3%] or < 75 years [RRR=42%; ARR= 5.2%]; with prevalent vertebral fracture [RRR= 35%] or prior non-vertebral fracture [RRR= 34%]; past osteoporotic treatment [RRR=48%] or without previous osteoporotic medication [RRR=35%] (all $p < 0.0001$). • No significant differences observed among the subjects receiving denosumab regardless of fragility fracture incidence, age subgroups, fracture site and past osteoporotic treatment history (all $p > 0.05$). • Denosumab treatment did not increase the adverse events, including serious, fatal cases or any discontinuation due to adverse effects compared to placebo.

(Continued)

Table 1 (Continued).

No.	Reference	Study Design	Subjects	Intervention Description	Outcomes
15	Cosman et al 2016 ⁴²	An international, randomized, double-blind, placebo-controlled, phase 3 fracture study on Japanese postmenopausal women with osteoporosis [FRacture study in postmenopausal woMen with osteoporosis (FRAME) study]; (ClinicalTrials.gov: NCT01575834)	A total of 7180 Japanese postmenopausal women, age 55–90 years with osteoporosis (BMD T-score -3.5 to -2.5 at total hip or femoral neck).	Subjects were randomized 1:1 to receive subcutaneous romosozumab 210 mg (N=3589) or placebo (N=3591) once monthly for 12 months. All subjects were transitioned to open-label denosumab 60 mg subcutaneously every 6 months for the first 12 months. All subjects received a minimum daily calcium (500–1000 mg) and vitamin D (600–800 IU) supplementation throughout the study.	<ul style="list-style-type: none"> ↓ cumulative new vertebral fracture risk in the romosozumab-to-denosumab group compared to the placebo-to-denosumab group in the 2 years of study [RR=0.25; 95% CI 0.16–0.40; $p<0.001$]. No significant difference in non-vertebral and clinical fracture risk between 24 months of romosozumab-to-denosumab and placebo-to-denosumab group [all $p>0.05$]. The incidence of adverse events through 24 months was similar between the romosozumab-to-denosumab and placebo-to-denosumab groups.
16	Miyauchi et al. 2019 ⁴³	Sub-group analysis of FRAME data	A total of 492 Japanese postmenopausal women, age 55–90 years with osteoporosis (BMD T-score -3.5 to -2.5 at total hip or femoral neck) were used in this FRAME sub-analysis with a total of 7180 subjects.	Subjects were randomized 1:1 to receive subcutaneous romosozumab 210 mg (N=190) or placebo (N=209) once monthly for 12 months. All subjects were transitioned to open-label denosumab 60 mg subcutaneously every 6 months for another 24 months. All subjects were prescribed a minimum daily calcium (500–1000 mg) and vitamin D (600–800 IU) supplementation throughout the study.	<ul style="list-style-type: none"> New vertebral fracture risk between romosozumab-to-denosumab and placebo-to-denosumab group was similar throughout these 3 years of study [all $p>0.05$]. Clinical, non-vertebral, major non-vertebral, major osteoporotic, clinical new or worsening vertebral and hip fracture risks were similar between 36 months of romosozumab-to-denosumab and placebo-to-denosumab group [all $p>0.05$]. The incidences of adverse events through 36 months were similar between the romosozumab-to-denosumab and placebo-to-denosumab groups (87.8% vs 89.8%, respectively).
17	Nakamura et al. 2014 ⁴¹	A randomized, double-blind, placebo-controlled trial on Japanese postmenopausal women and men with osteoporosis [Denosumab fracture Intervention Randomized placebo Controlled Trial (DIRECT)]; (ClinicalTrials.gov: NCT00680953)	A total of 1034 Japanese postmenopausal women and men aged 50 years or older with osteoporosis (BMD T-score <-1.7 (lumbar spine) or <-1.6 (total hip) with one to four prevalent vertebral fractures completed the study.	Subjects were randomly assigned in a 2:2:1 ratio to either receive placebo (N=416), denosumab 60 mg subcutaneous every 6 months (N=414), or open-label oral alendronate 35 mg weekly (N=204) for 24 months. At least 600 mg calcium and 400 IU vitamin D were supplemented daily throughout the study period.	<ul style="list-style-type: none"> ↓ risk of new or worsening vertebral fracture by 65.7% [HR= 0.343; 95% CI 0.194–0.606; $p=0.0001$] and new vertebral fracture by 74.0% [HR= 0.273; 95% CI 0.136–0.553; $p=0.0001$] in all respondents as compared to placebo after 24 months. ↓ risk of new or worsening vertebral fracture by 63.2% in postmenopausal women [HR= 0.368; 95% CI 0.207–0.653 $p=0.004$]. The 24-month denosumab did not significantly alter the risk of non-vertebral fracture and major non-vertebral fracture (all $p>0.05$) but significantly ↓ the risk of non-major non-vertebral fracture (2.5%) as compared to placebo (0.4%) ($p<0.05$). The 24-month denosumab therapy was well tolerated with no obvious difference in adverse events, serious adverse events or fatality between denosumab and placebo. ↑ incidence of adverse events including hypocalcaemia (+0.4%), bacterial cellulitis (+0.7%), infection (+4.3%) and cardiovascular disorder (+1.2%).

18	Grant et al, 2015 ⁴⁰	A prospective, double-blind, placebo-controlled, multicentre phase 3 study on postmenopausal women with hormone receptor-positive breast cancer and aromatase inhibitor as treatment [Austrian Breast Cancer Study Group (ABCSS-18); (ClinicalTrials.gov: NCT00556374)]	A total of 3420 postmenopausal women with early-stage hormone receptor-positive breast cancer and underwent aromatase inhibitor treatment completed the study.	Subjects received either 60 mg subcutaneous denosumab (N=1274) or placebo (N=1188) every 6 months up to 7 years with a median time of study of 38 months. Daily administration of 500 mg calcium and at least 400 IU vitamin D were supplemented throughout the study period.	<ul style="list-style-type: none"> ● Delayed the first clinical fracture [HR= 0.5; 95% CI 0.39–0.65; $p < 0.0001$] which was independent to BMD T-score with the estimated first clinical fracture of 5% (placebo 9.6%) and 11.1% (placebo 26.2%) at 36 and 84 months, respectively. ● ↓ new vertebral fracture [OR= 0.53; 95% CI 0.33–0.85; $p = 0.009$] and new or worsening vertebral fracture incidence [OR= 0.54; 95% CI 0.34–0.84; $p = 0.007$] after 36 months. ● The incidences of adverse events and serious adverse events were similar between the denosumab (80% and 30%, respectively) and placebo group (79% and 30%, respectively). ● No neutralizing anti-denosumab antibodies were identified in plasma samples at any time point.
19	Saag et al, 2018 ⁴⁴	A phase 3, international, randomized, double-blind, double-dummy, active-controlled, non-inferiority study on glucocorticoid-initiating and glucocorticoid-continuing patients (ClinicalTrials.gov: NCT01575873)	A total of 691 glucocorticoid-treated participants with osteoporosis (BMD T-score ≤ -2.0 or ≤ -1.0 with fracture history) or past osteoporosis-related fracture history.	Subjects with glucocorticoid therapy for < 3 months before screening was grouped as "glucocorticoid-initiating group" (N=253) while those with > 3 months therapy were grouped as "glucocorticoid-continuing group" (N=438). Subjects were then randomized 1:1 within each group to receive either subcutaneous denosumab 60 mg every 6 months and oral placebo daily for 12 months, or oral risedronate 5 mg daily with subcutaneous placebo every 6 months for 12 months. All patients were assigned to receive daily supplementation with at least 1000 mg calcium and 800 IU vitamin D.	<ul style="list-style-type: none"> ● The fracture incidences were found similar between 12 months risedronate and denosumab treatment including osteoporosis-related fractures (denosumab 7% vs risedronate 6%), new and worsening vertebral fractures (denosumab 1% vs risedronate 3% in men only; denosumab 4% vs risedronate 5% in women only; denosumab 0% vs risedronate 3% in premenopausal women only; both 5% in postmenopausal women only) and low-trauma non-vertebral fractures (denosumab 4% vs risedronate 3%). ● The 12-month denosumab was comparable with risedronate in reducing glucocorticoid-induced osteoporosis. ● Similar anti-osteoporosis effect by denosumab can be observed as early as 6 months treatment for both "glucocorticoid-continuing group" and "glucocorticoid-initiating group". ● Adverse events, serious adverse events, fractures and discontinuation of the study were similar between denosumab and risedronate.

(Continued)

Table 1 (Continued).

No.	Reference	Study Design	Subjects	Intervention Description	Outcomes
20	Saag et al, 2019 ⁴⁵	A phase 3, international, randomized, double-blind, double-dummy, active-controlled, parallel-group study on glucocorticoid-initiating and glucocorticoid-continuing patients (ClinicalTrials.gov: NCT01575873)	A total of 590 glucocorticoid-treated participants with osteoporosis (BMD T-score ≤ -2.0 or ≤ -1.0 with fracture history) or past osteoporosis-related fracture history.	Same as Saag et al 2018 but with 226 subjects in "glucocorticoid-initiating group" and 364 subjects in "glucocorticoid-continuing group" up to 24 months of treatment.	<ul style="list-style-type: none"> The fracture incidences for any osteoporosis-related fractures (denosumab 8.8% vs risedronate 9.1%), new and worsening vertebral fractures (denosumab 4.4% vs risedronate 6.9% for all subjects; denosumab 1.0% vs risedronate 5.0% in men only; denosumab 5.9% vs risedronate 7.8% in women only; denosumab 6.1% vs risedronate 6.9% in premenopausal women only; denosumab 5.9% vs risedronate 7.6% in postmenopausal women only) and low-trauma non-vertebral fractures (denosumab 5.3% vs risedronate 3.8%) were statistically similar for both denosumab and risedronate groups upon 24 months of treatment. Anti-osteoporotic effect of denosumab was reported at earlier time points (6 and 12 months) on both "glucocorticoid-continuing group" and "glucocorticoid-initiating group". The incidences of adverse events, fatality, infection and discontinuation of the study were similar between denosumab and risedronate.
21	Behanova et al (2019) ²⁵	A retrospective cohort study on Austria national data with propensity score matching for antiresorptive-treated and untreated patients	Previous data from a total of 47,139 patients aged ≥ 50 years old who experienced a hip fracture between January 2012 and December 2016 and follow-up with or without treatment (bisphosphonates or denosumab).	Hip fracture patients either received oral or intravenous bisphosphonates (N= 3789), denosumab (N=555) or no treatment (N=42,795), up to 60 months. However, the treatment dosage and interval are unknown.	<ul style="list-style-type: none"> There was higher risk of a subsequent hip fracture for denosumab-treated patients as compared to untreated patients [subdistribution hazard ratio, SHR= 1.67; 95% CI 1.04–2.66; $p < 0.05$], especially on women [SHR= 1.77; 95% CI 1.08–2.91; $p < 0.05$] but not on men subgroup [SHR= 0.93; 95% CI 0.22–4.05; $p > 0.05$]. No significant difference in subsequent hip fracture risk was detected between denosumab and bisphosphonate groups (oral and intravenous; all $p > 0.05$). Significantly lower risk of mortality by 26% on denosumab-treated patients was detected as compared with untreated patients [HR= 0.74; 95% CI 0.58–0.94; $p < 0.05$] but similar as with those bisphosphonate groups. Similar lower risk of mortality result was reported on denosumab-treated men [HR= 0.465; 95% CI 0.24–0.85; $p < 0.05$] but not women [HR= 0.81; 95% CI 0.62–1.06; $p > 0.05$].

<p>22</p> <p>Pedersen, Heide-Jorgensen, Sorensen, Prieto-Alhambra, and Ehrenstein, 2019²⁶</p>	<p>A retrospective cohort study using a nationwide, population-based, historical cohort study from Danish health registries/database with complete follow-up</p>	<p>Previous data from a total of 92,355 subjects aged ≥ 50 years who received the first dispensing of denosumab or alendronate from May 2010 to December 2017 without any antioosteoporosis medication within 1 year.</p>	<p>Patients either received denosumab (N=4624) or alendronate (N=87,731) and then followed-up up to 7.5 years (median= 3.3 years). However, the treatment dosage and interval are unknown.</p>	<ul style="list-style-type: none"> ● Within the first 3 years of follow-up, initiation of denosumab was associated with a similar risk on the hip or any fracture as alendronate [adjusted hazard ratio (aHR)=1.08; 95% CI 0.92–1.28]. ● The risk of hip fracture was similar between denosumab and alendronate in each subpopulation including male [aHR=1.24, 95% CI 0.79–1.95], female [aHR=1.03; 95% CI 0.87–1.22], <80 years [aHR=1.00; 95% CI 0.78–1.28], ≥80 years [aHR=1.21; 95% CI 0.97–1.51], those with history of any fracture [aHR=1.07; 95% CI 0.85–1.34], those without any fracture [aHR=1.05; 95% CI 0.83–1.32], those with previous hip fracture [aHR=1.25; 95% CI 0.89–1.76] and those without previous hip fracture [aHR=1.04; 95% CI 0.86–1.26]. ● The risk of any fracture was similar between denosumab and alendronate for men [aHR=0.96, 95% CI 0.68–1.36], ≥80 years [aHR=1.06; 95% CI 0.89–1.26] and those with previous hip fracture [aHR=1.11; 95% CI 0.85–1.44]. The risk of any fracture was slightly lower in denosumab group as compared with alendronate especially for women [aHR=0.89; 95% CI 0.88–0.99], <80 years [aHR=0.85; 95% CI 0.75–0.97], those with history of any fracture [aHR=0.84; 95% CI 0.71–0.98], those without any fracture [aHR=0.77; 95% CI 0.64–0.93], and those without previous hip fracture [aHR=0.89; 95% CI 0.79–0.99].
--	--	---	--	--

Notes: ¹Increase; ²Decrease.

Abbreviations: aHR, adjusted hazard ratio; ARR, absolute risk reduction; BMD, bone mass density, BMI, body mass index; CI, confidence interval; CKD, chronic kidney disease; HR, hazard ratio; OR, odds ratio; NA, not available; RR, relative risk; RRR, relative risk reduction; SHR, subdistribution hazard ratio.

In terms of the adverse reaction, denosumab did not significantly increase the total incidence of adverse effects including infection, cancer, hypocalcaemia, cardiovascular and peripheral vascular diseases, stroke, heart diseases. No cases of study discontinuation due to adverse events were reported.²⁸ All and serious adverse events remained stable over time in both denosumab and placebo groups during DIRECT, FREEDOM and FREEDOM extension studies.^{27,30,31,41} Additionally, denosumab is also safe regardless of age groups, kidney function, fragility fracture history, as well as in patients with breast cancer treated with an aromatase inhibitor.^{30,35,36,40,48} No event of osteonecrosis or neutralising anti-denosumab antibodies was identified.^{27,28,40,81} Histological examination of 22 samples from the 10-year denosumab-treated group revealed that all lamellar bones were normally mineralized with no pathological changes and low remodeling activation.²⁷

Denosumab, however, did slightly increase the incidence of certain adverse events including hypocalcaemia, bacterial cellulitis, infection, cardiovascular disorder, bone pain, pain in extremity, hot flush, hypertension, osteoarthritis and nervous system disorders in some subjects.^{40,41} Denosumab was also associated with a marginally higher incidence of eczema, flatulence and cellulitis among some FREEDOM subjects.²⁸ These adverse events, however, became insignificant during the 10-year FREEDOM extension study.²⁷ The adverse events and serious adverse events were found similar between denosumab and risedronate groups among glucocorticoid-treated subjects up to 24 months of treatment.^{44,45} Denosumab did marginally (~1%) increase the incidence of adverse events including back pain, hypertension, osteoporosis-related fractures and non-vertebral fractures compared to risedronate, but the statistical analysis was not performed.⁴⁴

Conclusion

Denosumab prevents the binding of RANKL to RANK on osteoclasts, thereby preventing bone loss through resorption and lowering the fracture risk. Through the clinical trials conducted, especially FREEDOM and its extension, denosumab demonstrates efficacy in preventing vertebral and non-vertebral fractures even with 10 years of continuous treatment. The performance of denosumab is on par with other treatment agents for osteoporosis like bisphosphonates. It is also safe to be used among vulnerable patients with chronic kidney disease and breast cancer treated with an aromatase inhibitor. Its hypocalcemic effects may require the physicians

to assess the calcium status of the patients before initiating treatment. Rebound bone loss and fracture risk after discontinuation is a concern, but this can be overcome by subsequent treatment with other agents like bisphosphonates. Since the efficacy of denosumab in preventing fracture is only assessed in limited studies, more comprehensive trials involving patients of diverse genetics and environmental exposure background are warranted.

Acknowledgments

The authors thank Universiti Kebangsaan Malaysia for funding them via Fundamental Research Grant (FF-2020-145). Dr. Kok-Lun Pang is a postdoctoral researcher funded by Universiti Kebangsaan Malaysia through Postdoctoral Research Scheme (RGA1).

Disclosure

The authors report no conflicts of interest in this work.

References

- Chin KY, Kamaruddin AA, Low NY, Ima-Nirwana S. Effects of age, sex, and ethnicity on bone health status of the elderly in Kuala Lumpur, Malaysia. *Clin Interventions Aging*. 2016;11:767-773. doi:10.2147/CIA.S108772
- World Health Organization. *WHO Scientific Group on the Assessment of Osteoporosis at Primary Health Care Level*. Belgium May: Brussels; 2004:5-7.
- Blain H, Masud T, Dargent-Molina P, et al. A comprehensive fracture prevention strategy in older adults: the European Union Geriatric Medicine Society (EUGMS) statement. *J Nutr Health Aging*. 2016;20(6):647-652. doi:10.1007/s12603-016-0741-y
- Rau CS, Lin TS, Wu SC, et al. Geriatric hospitalizations in fall-related injuries. *Scandinavian J Trauma, Resuscitation Emergency Med*. 2014;22:63. doi:10.1186/s13049-014-0063-1
- Matityahu A, Elson J, Morshed S, Marmor M. Survivorship and severe complications are worse for octogenarians and elderly patients with pelvis fractures as compared to adults: data from the national trauma data bank. *J Osteoporos*. 2012;2012:475739. doi:10.1155/2012/475739
- Ong T, Kantachavesiri P, Sahota O, Gladman JRF. Characteristics and outcomes of hospitalized patients with vertebral fragility fractures: a systematic review. *Age Ageing*. 2018;47(1):17-25. doi:10.1093/ageing/afx079
- Bauer K, Schwarzkopf L, Graessel E, Holle R. A claims data-based comparison of comorbidity in individuals with and without dementia. *BMC Genetics*. 2014;14:10.
- Madhavan MV, Gersh BJ, Alexander KP, Granger CB, Stone GW. Coronary artery disease in patients ≥ 80 years of age. *J Am Coll Cardiol*. 2018;71(18):2015-2040. doi:10.1016/j.jacc.2017.12.068
- Nazrun AS, Tzar MN, Mokhtar SA, Mohamed IN. A systematic review of the outcomes of osteoporotic fracture patients after hospital discharge: morbidity, subsequent fractures, and mortality. *Therapeutics Clin Risk Management*. 2014;10:937-948. doi:10.2147/TCRM.S72456
- Yoo J-I, Ha Y-C, Park KS, Kim R-B, Seo S-H, Koo K-H. Incidence and mortality of osteoporotic refractures in Korea according to nationwide claims data. *Yonsei Med J*. 2019;60(10):969-975. doi:10.3349/ymj.2019.60.10.969

11. Cosman F, de Beur SJ, LeBoff MS, et al. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis Int.* 2014;25(10):2359–2381. doi:10.1007/s00198-014-2794-2
12. Unnanuntana A, Gladnick BP, Donnelly E, Lane JM. The assessment of fracture risk. *J Bone Joint Surgery. American Volume.* 2010;92(3):743–753. doi:10.2106/JBJS.I.00919
13. Chen YC, Lin WC. Poor 1st-year adherence to anti-osteoporotic therapy increases the risk of mortality in patients with magnetic resonance imaging-proven acute osteoporotic vertebral fractures. *Patient Preference Adherence.* 2017;11:839–843. doi:10.2147/PPA.S131564
14. Lems WF, Raterman HG. Critical issues and current challenges in osteoporosis and fracture prevention. An overview of unmet needs. *Therapeutic Adv Musculoskeletal Disease.* 2017;9(12):299–316. doi:10.1177/1759720X17732562
15. van den Bergh JP, van Geel TA, Geusens PP. Osteoporosis, frailty and fracture: implications for case finding and therapy. *Nature Reviews. Rheumatology.* 2012;8(3):163–172. doi:10.1038/nrrheum.2011.217
16. Kostenuik PJ, Nguyen HQ, McCabe J, et al. Denosumab, a fully human monoclonal antibody to RANKL, inhibits bone resorption and increases BMD in knock-in mice that express chimeric (murine/human) RANKL. *J Bone Mineral Res.* 2009;24(2):182–195. doi:10.1359/jbmr.081112
17. Kearns AE, Khosla S, Kostenuik PJ. Receptor activator of nuclear factor kappaB ligand and osteoprotegerin regulation of bone remodeling in health and disease. *Endocrine Reviews.* 2008;29(2):155–192.
18. Lewiecki EM, Bilezikian JP. Denosumab for the treatment of osteoporosis and cancer-related conditions. *Clin Pharmacology Therapeutics.* 2012;91(1):123–133. doi:10.1038/clpt.2011.268
19. Sanchez A, Brun LR, Salerni H, et al. Effect of denosumab on bone mineral density and markers of bone turnover among postmenopausal women with osteoporosis. *J Osteoporos.* 2016;2016:8738959. doi:10.1155/2016/8738959
20. Deeks ED. Denosumab: a review in postmenopausal osteoporosis. *Drugs Aging.* 2018;35(2):163–173. doi:10.1007/s40266-018-0525-7
21. Tsourdi E, Langdahl B, Cohen-Solal M, et al. Discontinuation of denosumab therapy for osteoporosis: a systematic review and position statement by ECTS. *Bone.* 2017;105:11–17. doi:10.1016/j.bone.2017.08.003
22. Yanbey ZA, Hansen KE. Denosumab in the treatment of glucocorticoid-induced osteoporosis: a systematic review and meta-analysis. *Drug Design, Development Therapy.* 2019;13:2843–2852. doi:10.2147/DDDT.S148654
23. Bridgeman MB, Pathak R. Denosumab for the reduction of bone loss in postmenopausal osteoporosis: a review. *Clin Therapeutics.* 2011;33(11):1547–1559. doi:10.1016/j.clinthera.2011.10.008
24. Wensel TM, Iranikah MM, Wilborn TW. Effects of denosumab on bone mineral density and bone turnover in postmenopausal women. *Pharmacotherapy.* 2011;31(5):510–523. doi:10.1592/phco.31.5.510
25. Behanova M, Reichardt B, Stamm TA, Zwerina J, Klaushofer K, Kocivan R. Treatment effects of bisphosphonates and denosumab on survival and refracture from real-world data of hip-fractured patients. *Calcif Tissue Int.* 2019;105(6):630–641. doi:10.1007/s00223-019-00611-3
26. Pedersen AB, Heide-Jorgensen U, Sorensen HT, Prieto-Alhambra D, Ehrenstein V. Comparison of risk of osteoporotic fracture in denosumab vs alendronate treatment within 3 years of initiation. *JAMA Network Open.* 2019;2(4):e192416. doi:10.1001/jamanetworkopen.2019.2416
27. Bone HG, Wagman RB, Brandi ML, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomized FREEDOM trial and open-label extension. *Lancet Diab Endocrinol.* 2017;5(7):513–523. doi:10.1016/S2213-8587(17)30138-9
28. Cummings SR, San Martin J, McClung MR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *New England J Med.* 2009;361(8):756–765. doi:10.1056/NEJMoa0809493
29. Ferrari S, Adachi JD, Lippuner K, et al. Further reductions in non-vertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. *Osteoporosis Int.* 2015;26(12):2763–2771. doi:10.1007/s00198-015-3179-x
30. Papapoulos S, Chapurlat R, Libanati C, et al. Five years of denosumab exposure in women with postmenopausal osteoporosis: results from the first two years of the FREEDOM extension. *J Bone Mineral Res.* 2012;27(3):694–701. doi:10.1002/jbmr.1479
31. Papapoulos S, Lippuner K, Roux C, et al. The effect of 8 or 5 years of denosumab treatment in postmenopausal women with osteoporosis: results from the FREEDOM Extension study. *Osteoporosis Int.* 2015;26(12):2773–2783. doi:10.1007/s00198-015-3234-7
32. Bilezikian JP, Lin CJF, Brown JP, et al. Long-term denosumab treatment restores cortical bone loss and reduces fracture risk at the forearm and humerus: analyses from the FREEDOM Extension cross-over group. *Osteoporosis Int.* 2019;30(9):1855–1864. doi:10.1007/s00198-019-05020-8
33. Kendler DL, Chines A, Brandi ML, et al. The risk of subsequent osteoporotic fractures is decreased in subjects experiencing fracture while on denosumab: results from the FREEDOM and FREEDOM Extension studies. *Osteoporosis Int.* 2019;30(1):71–78. doi:10.1007/s00198-018-4687-2
34. Austin M, Yang YC, Vittinghoff E, et al. Relationship between bone mineral density changes with denosumab treatment and risk reduction for vertebral and non-vertebral fractures. *J Bone Mineral Res.* 2012;27(3):687–693. doi:10.1002/jbmr.1472
35. Boonen S, Adachi JD, Man Z, et al. Treatment with denosumab reduces the incidence of new vertebral and hip fractures in postmenopausal women at high risk. *J Clin Endocrinol Metabolism.* 2011;96(6):1727–1736. doi:10.1210/jc.2010-2784
36. Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Mineral Res.* 2011;26(8):1829–1835. doi:10.1002/jbmr.403
37. McCloskey EV, Johansson H, Oden A, et al. Denosumab reduces the risk of osteoporotic fractures in postmenopausal women, particularly in those with moderate to high fracture risk as assessed with FRAX. *J Bone Mineral Res.* 2012;27(7):1480–1486. doi:10.1002/jbmr.1606
38. McClung MR, Boonen S, Torring O, et al. Effect of denosumab treatment on the risk of fractures in subgroups of women with postmenopausal osteoporosis. *J Bone Mineral Res.* 2012;27(1):211–218. doi:10.1002/jbmr.536
39. Simon JA, Recknor C, Moffett AH Jr, et al. Impact of denosumab on the peripheral skeleton of postmenopausal women with osteoporosis: bone density, mass, and strength of the radius, and wrist fracture. *Menopause.* 2013;20(2):130–137. doi:10.1097/GME.0b013e318267f909
40. Gnant M, Pfeiler G, Dubsy PC, et al. Adjuvant denosumab in breast cancer (ABCSG-18): a multicentre, randomized, double-blind, placebo-controlled trial. *Lancet.* 2015;386(9992):433–443. doi:10.1016/S0140-6736(15)60995-3
41. Nakamura T, Matsumoto T, Sugimoto T, et al. Clinical trials express: fracture risk reduction with denosumab in Japanese postmenopausal women and men with osteoporosis: denosumab fracture intervention randomized placebo controlled trial (DIRECT). *J Clin Endocrinol Metabolism.* 2014;99(7):2599–2607. doi:10.1210/jc.2013-4175
42. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *New England J Med.* 2016;375(16):1532–1543. doi:10.1056/NEJMoa1607948
43. Miyauchi A, Dinavahi RV, Crittenden DB, et al. Increased bone mineral density for 1 year of romosozumab, vs placebo, followed by 2 years of denosumab in the Japanese subgroup of the pivotal FRAME trial and extension. *Arch Osteoporos.* 2019;14(1):59. doi:10.1007/s11657-019-0608-z

44. Saag KG, Wagman RB, Geusens P, et al. Denosumab versus risedronate in glucocorticoid-induced osteoporosis: a multicentre, randomized, double-blind, active-controlled, double-dummy, non-inferiority study. *Lancet Diab Endocrinol*. 2018;6(6):445–454. doi:10.1016/S2213-8587(18)30075-5
45. 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. doi:10.1002/art.40874
46. Bell AD, Bell BR. The FREEDOM trial is family medicine ready for biologic therapies? *Canadian Family Physician • Le Médecin De Famille Canadien*. 2011;57:438–441.
47. ClinicalTrials.gov. A study to evaluate denosumab in the treatment of postmenopausal osteoporosis; 2020. Available from: <https://clinicaltrials.gov/ct2/show/record/NCT00089791>. Accessed March 9, 2020.
48. Palacios S, Kalouche-Khalil L, Rizzoli R, et al. Treatment with denosumab reduces secondary fracture risk in women with postmenopausal osteoporosis. *Climacteric*. 2015;18(6):805–812. doi:10.3109/13697137.2015.1045484
49. Lindsay R, Kregg JH, Marin F, Jin L, Stepan JJ. Teriparatide for osteoporosis: importance of the full course. *Osteoporosis Int*. 2016;27(8):2395–2410. doi:10.1007/s00198-016-3534-6
50. Dempster DW, Zhou H, Recker RR, et al. Differential effects of teriparatide and denosumab on intact PTH and bone formation indices: AVA osteoporosis study. *J Clin Endocrinol Metab*. 2016;101(4):1353–1363. doi:10.1210/jc.2015-4181
51. Deng J, Silver Z, Huang E, et al. Pharmacological prevention of fractures in patients undergoing glucocorticoid therapies: a systematic review and network meta-analysis. *Rheumatology*. 2020. doi:10.1093/rheumatology/keaa228
52. Tsai JN, Uihlein AV, Lee H, et al. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomized trial. *Lancet*. 2013;382(9886):50–56. doi:10.1016/S0140-6736(13)60856-9
53. Leder BZ, Tsai JN, Uihlein AV, et al. Two years of Denosumab and teriparatide administration in postmenopausal women with osteoporosis (The DATA Extension Study): a randomized controlled trial. *J Clin Endocrinol Metab*. 2014;99(5):1694–1700. doi:10.1210/jc.2013-4440
54. Vahle JL, Long GG, Sandusky G, Westmore M, Ma YL, Sato M. Bone neoplasms in F344 rats given teriparatide [rhPTH (1-34)] are dependent on duration of treatment and dose. *Toxicologic Pathology*. 2004;32(4):426–438. doi:10.1080/01926230490462138
55. Vahle JL, Sato M, Long GG, et al. Skeletal changes in rats given daily subcutaneous injections of recombinant human parathyroid hormone (1-34) for 2 years and relevance to human safety. *Toxicologic Pathology*. 2002;30(3):312–321. doi:10.1080/01926230252929882
56. Cosman F, Nieves JW, Zion M, et al. Daily or cyclical teriparatide treatment in women with osteoporosis on no prior therapy and women on alendronate. *J Clin Endocrinol Metab*. 2015;100(7):2769–2776. doi:10.1210/jc.2015-1715
57. Cosman F, McMahon D, Dempster D, Nieves JW. Standard versus cyclic teriparatide and denosumab treatment for osteoporosis: a randomized trial. *J Bone Mineral Res*. 2020;35(2):219–225. doi:10.1002/jbmr.3850
58. Leder BZ, Tsai JN, Uihlein AV, et al. Denosumab and teriparatide transitions in postmenopausal osteoporosis (the DATA-Switch study): extension of a randomized controlled trial. *Lancet*. 2015;386(9999):1147–1155. doi:10.1016/S0140-6736(15)61120-5
59. Tsai JN, Jiang LA, Lee H, Hans D, Leder BZ. Effects of teriparatide, denosumab, or both on spine trabecular microarchitecture in DATA-switch: a randomized controlled trial. *J Clin Densitometry*. 2017;20(4):507–512. doi:10.1016/j.jocd.2017.05.007
60. Guanabens N, Moro-Alvarez MJ, Casado E, et al. The next step after anti-osteoporotic drug discontinuation: an up-to-date review of sequential treatment. *Endocrine*. 2019;64(3):441–455. doi:10.1007/s12020-019-01919-8
61. Iranikhan M, Deas C, Murphy P, Freeman MK. Effects of denosumab after treatment discontinuation: A review of the literature. *Consultant Pharmacist*. 2018;33(3):142–151. doi:10.4140/TCP.n.2018.142
62. Bone HG, Bolognese MA, Yuen CK, et al. Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *J Clin Endocrinol Metab*. 2011;96(4):972–980. doi:10.1210/jc.2010-1502
63. Cummings SR, Ferrari S, Eastell R, et al. Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *J Bone Mineral Res*. 2017;33(2):190–198. doi:10.1002/jbmr.3337
64. McClung MR, Wagman RB, Miller PD, Wang A, Lewiecki EM. Observations following discontinuation of long-term denosumab therapy. *Osteoporosis Int*. 2017;28(5):1723–1732. doi:10.1007/s00198-017-3919-1
65. Sosa Henriquez M, Gómez de Tejada Romero MJ, Escudero-Socorro M, et al. Hip fractures following denosumab discontinuation: three clinical cases reports. *J Royal Soc Med*. 2019;112(11):472–475. doi:10.1177/0141076819861027
66. Tripto-Shkolnik L, Fund N, Rouach V, Chodick G, Shalev V, Goldshtein I. Fracture incidence after denosumab discontinuation: real-world data from a large healthcare provider. *Bone*. 2020;130:115150. doi:10.1016/j.bone.2019.115150
67. Miller PD, Wagman RB, Peacock M, et al. Effect of denosumab on bone mineral density and biochemical markers of bone turnover: six-year results of a Phase 2 clinical trial. *J Clin Endocrinol Metabolism*. 2011;96(2):394–402. doi:10.1210/jc.2010-1805
68. Anastasilakis AD, Evangelatos G, Makras P, Iliopoulos A. Rebound-associated vertebral fractures may occur in sequential time points following denosumab discontinuation: need for prompt treatment re-initiation. *Bone Reports*. 2020;12:100267. doi:10.1016/j.bonr.2020.100267
69. Gonzalez-Rodriguez E, Aubry-Rozier B, Stoll D, Zaman K, Lamy O. Sixty spontaneous vertebral fractures after denosumab discontinuation in 15 women with early-stage breast cancer under aromatase inhibitors. *Breast Cancer Res Treatment*. 2020;179(1):153–159. doi:10.1007/s10549-019-05458-8
70. Niimi R, Kono T, Nishihara A, Hasegawa M, Kono T, Sudo A. Second rebound-associated vertebral fractures after denosumab discontinuation. *Arch Osteoporos*. 2020;15(1):7. doi:10.1007/s11657-019-0676-0
71. Anastasilakis AD, Makras P. Multiple clinical vertebral fractures following denosumab discontinuation. *Osteoporosis Int*. 2016;27(5):1929–1930. doi:10.1007/s00198-015-3459-5
72. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Mineral Res*. 2017;32(6):1291–1296. doi:10.1002/jbmr.3110
73. Anastasilakis AD, Yavropoulou MP, Makras P, et al. Increased osteoclastogenesis in patients with vertebral fractures following discontinuation of denosumab treatment. *European J Endocrinol*. 2017;176(6):677–683. doi:10.1530/EJE-16-1027
74. Fassio A, Adami G, Benini C, et al. Changes in Dkk-1, sclerostin, and RANKL serum levels following discontinuation of long-term denosumab treatment in postmenopausal women. *Bone*. 2019;123:191–195. doi:10.1016/j.bone.2019.03.019
75. Jahn-Rickert K, Wolfel EM, Jobke B, et al. Elevated bone hardness under denosumab treatment, with persisting lower osteocyte viability during discontinuation. *Front Endocrinol*. 2020;11:250. doi:10.3389/fendo.2020.00250
76. Miller PD, Bolognese MA, Lewiecki EM, et al. Effect of denosumab on bone density and turnover in postmenopausal women with low bone mass after long-term continued, discontinued, and restarting of therapy: a randomized blinded phase 2 clinical trial. *Bone*. 2008;43(2):222–229. doi:10.1016/j.bone.2008.04.007

77. Laroche M, Couture G, Ruysen-Witrand A, Constantin A, Degboe Y. Effect of risedronate on bone loss at discontinuation of denosumab. *Bone Reports*. 2020;13:100290. doi:10.1016/j.bonr.2020.100290
78. Adami G, Giollo A, Rossini M, et al. Different fracture risk profile in patients treated with anti-osteoporotic drugs in real-life. *Reumatismo*. 2020;72(2):71–74. doi:10.4081/reumatismo.2020.1267
79. Kendler D, Chines A, Clark P, et al. Bone mineral density after transitioning from denosumab to alendronate. *J Clin Endocrinol Metab*. 2020;105:3. doi:10.1210/clinem/dgz095
80. Uebelhart B, Rizzoli R, Ferrari SL. Retrospective evaluation of serum CTX levels after denosumab discontinuation in patients with or without prior exposure to bisphosphonates. *Osteoporosis Int*. 2017;28(9):2701–2705. doi:10.1007/s00198-017-4080-6
81. Wilcken N, Inkyung Lee C. In postmenopausal women with breast cancer treated with aromatase inhibitors, denosumab reduced fractures. *Annals of Internal Medicine*. 2015;163(6):Jc11. doi:10.7326/ACPJC-2015-163-6-011

Drug Design, Development and Therapy

Dovepress

Publish your work in this journal

Drug Design, Development and Therapy is an international, peer-reviewed open-access journal that spans the spectrum of drug design and development through to clinical applications. Clinical outcomes, patient safety, and programs for the development and effective, safe, and sustained use of medicines are a feature of the journal, which has also

been accepted for indexing on PubMed Central. The manuscript management system is completely online and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/drug-design-development-and-therapy-journal>