

From Evidence to Practice: Denosumab in Osteoporosis and Joint Health

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ABSTRACT

Osteoporosis and osteopenia are prevalent conditions in India, particularly among postmenopausal women and the elderly, leading to increased fracture risks and morbidity. Denosumab, a monoclonal antibody, demonstrates superior efficacy over other treatments in reducing fracture risk and enhancing bone mineral density (BMD). Clinical trials highlight its effectiveness in preventing periprosthetic bone loss, improving implant stability, and mitigating femoral head collapse in various conditions; combination therapies involving denosumab further amplify BMD gains and reduce fracture risk. The article reviews the efficacy and safety of denosumab in managing osteoporosis, joint replacement therapy, and avascular necrosis based on a review of clinical evidence and studies. Denosumab emerges as a cornerstone therapy for osteoporosis management, offering multifaceted benefits in fracture prevention, joint replacement therapy, and avascular necrosis.

Keywords: Osteoporosis, osteopenia, fracture, denosumab, joint replacement therapy, avascular necrosis

Almost 1 out of 2 adults in India have osteopenia, and 1 out of 5 have osteoporosis. It is reported that osteoporosis prevalence is higher in women compared to the elderly. Almost 1 out of 3 women in postmenopausal age group have osteoporosis.

The prevalence of osteoporosis is similar across the four zones of India¹. Additionally, the prevalence of osteopenia was found to be higher in women (40.3%) than men (29.9%)².

In a study from Punjab, India, the prevalence of osteoporosis and osteopenia in postmenopausal women was seen to be 30.5% and 44.2%, respectively³.

It has been suggested that hip fractures will increase to more than 1 million with a male-to-female ratio of 1:3⁴. Loss of bone leads to reduced compressive and/or torsional strength and increases the risk of fragility fractures, especially in the aging population. Considering this significant burden, early identification and management of osteopenia and osteoporosis are essential to reduce the burden of fracture¹. Hence, this expert consensus statement is developed to provide a comprehensive review and synthesis of current clinical evidence and studies pertaining to the efficacy, safety, and practical applications of denosumab in the management of osteoporosis, joint replacement therapy, and avascular necrosis.

METHODOLOGY

The objective of the above consensus is to review denosumab's efficacy, safety, and practical applications and offer recommendations based on clinical evidence and consensus among the panelists.

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In the first stage, a systematic literature review was conducted, including articles on denosumab's efficacy and safety from January 2005 to January 2024. The articles included randomized clinical trials, systematic reviews and meta-analyses, and narrative reviews. Concurrent with the initial literature search, a list of indications for denosumab was decided, these included osteoporosis, joint replacement therapy, and avascular necrosis. A 12-member expert panel was then formed, the selection criteria being their medical specialty, research, and clinical experience in the field of interest, and relevance to the agenda discussions. A 2-day meeting was conducted with the panelists to discuss the objectives of the consensus meeting. All the panelists were given pre-read materials, a list of selected indications, and a compilation of literature selected after the literature search. Following the meeting, the given themes were selected: osteoporosis and denosumab, joint replacement therapy and denosumab, avascular necrosis and osteoporosis, and combination therapy with denosumab. The manuscript was developed and shared with all the panel members for their review and feedback.

OSTEOPOROSIS AND DENOSUMAB

Denosumab is a human monoclonal IgG2 antibody with a high affinity and specificity for human receptor activators of nuclear factor kappa- β ligand (RANKL), the principal regulator of osteoclastic bone resorption. Denosumab binds to RANKL, preventing RANKL from activating its receptor, RANK, on formation, function, and survival, thereby reducing bone resorption⁵.

Clinical Evidence

The results of FREEDOM (Fracture REduction Evaluation of Denosumab in Osteoporosis every 6 Months) is a 3-year phase III trial that showed significant relative risk reduction for vertebral fractures (68%), hip fractures (40%), and nonvertebral fractures (20%) with the use of denosumab compared with placebo⁶. The results of the FREEDOM trial provided the base for the Food and Drug Administration (FDA) approval of denosumab for the treatment of postmenopausal women with osteoporosis at high risk for fracture⁵.

The results of the FREEDOM Extension trial (up to 8 years of therapy) showed a mean increase in bone mineral density (BMD) from baseline in the denosumab group, an 18.5% increase in the lumbar spine (LS), and an 8.2% increase in the total hip in the long-term group. It was also seen that after a further 5 years from the FREEDOM trial duration, new vertebral and

nonvertebral fracture rates remained low throughout the extension study period, with a hip fracture rate during year 8 of 0.2% in the long-term group and 0.1% in the crossover group⁷.

The results of the DECIDE (Determining Efficacy; Comparison of Initiating Denosumab vs. Alendronate) trial showed a significantly higher BMD increase at the total hip compared to alendronate (3.5% denosumab, 2.6% alendronate, $p < 0.0001$) at the end of 12 months of treatment. A treatment difference of 0.65 was observed at the femoral neck and 1.1% at LS⁸. Similar results were seen in the STAND (Study of Transitioning from Alendronate to Denosumab) trial, which investigated denosumab versus alendronate in individuals already being treated with alendronate. At the end of 12 months of therapy, a statistically significant increase in BMD with denosumab (1.9% increase) was seen compared with continuing alendronate (1.05% increase), $p < 0.0001$ ⁹.

Another comparative study of denosumab with risedronate in postmenopausal women who were treated with but suboptimally adherent to alendronate showed that after 12 months of therapy, denosumab led to a higher gain in BMD at total hip (2.0% denosumab, 0.5% risedronate), femoral neck (1.4% denosumab, 0% risedronate), and LS (3.4% denosumab, 1.1% risedronate), $p < 0.0001$ at all sites¹⁰.

In another study, ADAMO (A multicenter, randomized, double-blind, placebo-controlled study to compare the efficacy and safety of DenosumAb vs. placebo in Males with Osteoporosis), 12 months of therapy with denosumab resulted in a BMD increase of 5.7% at the LS, 2.4% at the total hip and 2.1% at the femoral neck. The results showed robust effects on further analyses controlling for baseline covariates, such as baseline testosterone levels, BMD T-scores and 10-year osteoporotic fracture risk. The results of this trial formed the basis of FDA approval for the use of denosumab in the treatment of men with osteoporosis at high risk of fracture¹¹.

The HALT (Hormone Ablation bone Loss Trial) provided results that led to the FDA approval of denosumab use in men undergoing androgen-deprivation therapy for nonmetastatic, hormone-sensitive prostate cancer. At 24 months of therapy, BMD of the LS had increased by 5.6% in the denosumab group as compared with a loss of 1.0% in the placebo group ($p < 0.001$); significant differences in the therapy were noted as early as 1 month and maintained through a period of 36 months. Individuals treated with denosumab had a reduced incidence of new vertebral fractures at 36 months¹².

Another randomized controlled trial of 2 years was conducted in women with hormone receptor-positive nonmetastatic breast cancer treated with adjuvant aromatase inhibitor therapy. This trial provided the ground for basing the FDA decision in approving denosumab use to increase bone mass in women at high risk for fracture receiving adjuvant aromatase inhibitor therapy for breast cancer. In the study, LS BMD increased by 5.5% at 12 months and 7.6% at 24 months higher in the denosumab group versus the placebo group ($p < 0.0001$ at both time points)¹³.

The Denosumab Adherence Preference Satisfaction (DAPS) study showed that less nonadherence to therapy was found in the denosumab group versus alendronate, and 92.4% of study participants showed a preference for denosumab over alendronate¹⁴.

Many clinical trials have also shown the reversibility of denosumab-mediated effects on bone. A phase 3 study showed that when individuals treated with denosumab for 2 years were followed for 24 months after discontinuation¹⁵.

JOINT REPLACEMENT THERAPY AND DENOSUMAB

Periprosthetic bone loss is a significant cause of aseptic loosening that leads to implant failure. It usually starts in the first postoperative year and gradually declines after 7 years¹⁶. Several medicines are suggested for the long-term survival of the implants, such as bisphosphonates¹⁷.

Denosumab is known to be the most powerful inhibitor of osteoclastic activity, with significantly high reductions of bone resorption. The reduction in serum levels of C-telopeptide was close to maximal within 3 days after dosing¹⁸. Denosumab can prevent periprosthetic bone loss after total hip arthroplasty, especially in Gruen zone 7; the BMD can be increased by as much as 7%¹⁹. Another study showed that denosumab increases the BMD of the proximal femur, administered for 6 to 12 months after surgery. This helps the bone to respond locally to prevent stem migration²⁰. In this study, the patients received denosumab subcutaneously, 60 mg once every 6 months for 12 months, starting a month before surgery. Denosumab significantly reduced bone loss in the medial femoral neck and increased periprosthetic BMD in the greater trochanteric and lesser trochanteric regions²⁰. Nagoya et al also showed that the denosumab given post-total knee arthroplasty significantly prevented early prosthetic bone loss and decreased periprosthetic tibial bone atrophy for up to 12 months¹⁹. Another study reported that denosumab

assisted in achieving better early stability and prognosis by significantly decreasing prosthetic bone loss in the early postoperative period²¹. Denosumab also reduces the early migration of the tibial part by reducing the total point motion. It leads to better early and long-term stability of the implant²². Denosumab persistently preserves the periprosthetic BMD after uncemented total hip arthroplasty¹⁵. In a 6-year-long study, where patients were scheduled for revision surgery for symptomatic osteolysis, it was seen that there were 83% fewer osteoclasts at the osteolysis membrane-bone interface in the denosumab group²³.

Achieving early stable fixation in total knee replacement is important to prevent late loosening. In a randomized controlled trial in patients undergoing total knee replacement, it was seen that denosumab reduces early migration by one-third and, hence, may be beneficial for long-term results. The study authors suggested that denosumab could also eliminate the need for most revisions due to aseptic loosening²².

COMBINATION THERAPY WITH DENOSUMAB

Treatment approaches that adopt the use of anabolic agents followed by potent antiresorptive therapies are highly efficacious in reducing fracture risk rapidly and leading to large BMD gains. The results of the FRActure study in postmenopausal woME n with osteoporosis (FRAME) study showed that individuals receiving bone-forming agent romosozumab for 12 months followed by 12 months of denosumab had a sustained reduction in fracture risk and a further increase in BMD in the 24 months treatment sequence²⁴ and an additional year of denosumab in the FRAME Extension study²⁵.

The Denosumab and Teriparatide Administration (DATA) study showed that at 12 months, LS BMD increased more in the denosumab and teriparatide combination group than in the teriparatide or denosumab groups. A similar result was seen in total-hip BMD (combination, 4.9% [2.9]; teriparatide, 0.7% [2.7], $p < 0.0001$; denosumab 2.5% [2.6], $p = 0.0011$)²⁶. Denosumab leads to more effective de-linking of bone resorption and formation. Denosumab also suppresses teriparatide-induced bone resorption while only partially decreasing it-induced bone formation⁵. In the DATA-Switch study, individuals treated with bone-forming teriparatide for 24 months and then switched to denosumab for 24 months experienced a significant increase in BMD. However, individuals who were randomized to receive denosumab as initial therapy for 24 months and then switched to teriparatide for

24 months experienced progressive or transient bone loss at the hip during teriparatide therapy, even though spine BMD increased²⁷. While there is no data as yet, it is suggested that patients who remain at high risk of fracture despite denosumab treatment should be given teriparatide additionally and continue denosumab²⁸.

Teriparatide and denosumab can be used sequentially in pulsating therapies. It has been seen that when used in sequential therapy of 6 months of teriparatide followed by 6 months of denosumab for 36 months, the hip radius and BMD benefits were better at 18 months follow-up, while no significant difference was observed at 36 months²⁹. Another study has also shown that when patients transitioned from bisphosphonate to denosumab or teriparatide, hip BMD increased with denosumab over 2 years, but no change was seen with teriparatide³⁰. In this study, the patients were treated with bisphosphonates for at least 12 months before they were switched to teriparatide or denosumab, and the follow-up was 6 to 27 months after the initiation of teriparatide or denosumab.

AVASCULAR OSTEONECROSIS AND DENOSUMAB

In a study on patients with steroid-induced osteonecrosis of the femoral head (ONFH), it was seen that denosumab had a positive effect on preventing femoral head collapse in patients with steroid ONFH. The effect is known to be associated with the inhibition of osteoclasts and their autophagy³¹. In a case report, it has been seen that denosumab can be used to normalize the bone-remodeling parameters in patients with bone alterations caused by radiotherapy³².

Recommendations for Denosumab Use in Clinical Practice

- Osteoporosis is a condition that requires long-term monitoring and treatment. The current published maximum follow-up time is 10 years, but there is no absolute limit on the treatment duration. The decision to continue denosumab has to be customized based on the variable BMD treatment targets, patient age, bisphosphonate tolerance, underlying comorbidities, and fall risk.
- Denosumab should be given 6 to 12 months prior to surgery and continued for 12 months to preserve bone structure and improve bone stability.

- Denosumab could be given postoperatively in joint replacement to prevent early bone resorption around the implants. If given, the recommendation is to administer two doses of denosumab (immediately after surgery and in 6 months) in patients undergoing joint replacement surgery.

CONCLUSION

The article underscores the significant prevalence of osteoporosis and osteopenia in India, particularly among postmenopausal women and the elderly; given the escalating incidence of fractures and associated morbidity, there is a need for effective management strategies. Denosumab is a pivotal therapeutic intervention backed by substantial clinical evidence. Denosumab showcases superiority over other treatments like alendronate and risedronate, emphasizing its role in enhancing BMD. Notably, denosumab also proves beneficial in joint replacement therapy, preventing periprosthetic bone loss and enhancing implant stability.

Additionally, in conditions like avascular osteonecrosis, denosumab exhibits promise in mitigating femoral head collapse. Combination therapies incorporating denosumab, such as romosozumab or teriparatide, amplify BMD gains and reduce fracture risk. Denosumab's multifaceted benefits in managing osteoporosis, joint replacement, and avascular necrosis underscore its pivotal role as a cornerstone in modern therapeutic approaches. The recommendations in the present review are based on the available evidence and clinical practice of the experts.

However, many experts are of the view that there is a need for further clinical research on the use of denosumab joint replacement therapy, its interaction with drugs it is combined with or substituted in the treatment of osteoporosis, and long-term use.

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