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Review Article

DENOSUMAB: A NEW ERA IN OSTEOPOROSIS MANAGEMENT IN VIETNAM

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ABSTRACT: Osteoporosis is a skeletal disorder characterized by compromised bone strength and increased fracture risk. In Vietnam, the disease affects ~30% in postmenopausal women and ~10% in men over 50, highlighting a growing public health challenge as the population ages. Bisphosphonates remain the standard first-line treatment. Recent advances in bone biology highlight the critical role of the RANK/RANKL/OPG pathway in bone remodeling. Osteoporosis arises when the RANKL/OPG ratio becomes imbalanced. Denosumab, a monoclonal antibody that targets RANKL, replicates OPG's ability to suppress osteoclast activity, increasing bone mineral density and reducing fracture risk by 20–68% across various skeletal sites. Unlike bisphosphonates, Denosumab is reversible, metabolized by the reticuloendothelial system, and appropriate for patients with advanced kidney disease, though it necessitates monitoring for hypocalcemia. This advancement offers clinicians a valuable tool for managing osteoporosis in Vietnam.

Keywords: osteoporosis, denosumab, RANKL/OPG

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1. THE MAGNITUDE OF OSTEOPOROSIS

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength, predisposing an individual to an increased risk of fracture (1). Bone strength is primarily determined by bone mineral density (BMD), measured via dual-energy X-ray absorptiometry (DXA), and bone quality, which includes factors such as bone architecture, turnover rates, microdamage accumulation, and mineralization. Osteoporosis is often termed a "silent disease" because bone loss progresses insidiously without symptoms until a fracture occurs, typically in the hip, spine, or wrist.

These fractures can lead to significant morbidity, including chronic pain, disability, reduced quality of life, and increased mortality, particularly following hip fractures (2). The one-year mortality following hip fracture ranges from 15% to 30% worldwide (3), and survivors frequently experience significant functional decline. Many patients never regain their pre-fracture level of mobility or independence. In Asia, where family-based care is common, the burden of caregiving often falls on family members, adding emotional and economic strain. Vertebral fractures, though sometimes clinically silent, can lead to chronic back pain, height loss, kyphosis, and impaired respiratory function, all of which can severely compromise quality of life (4).

Globally, osteoporosis represents a significant public health challenge, affecting over 200 million people worldwide (1). It is estimated that one in three women and one in five men over the age of 50 will sustain an osteoporotic fracture in their lifetime (5). The global burden is substantial, with osteoporotic fractures contributing to an estimated 9 million fractures annually, including 1.6 million hip fractures, which are associated with the highest morbidity and mortality. The economic impact is considerable, with costs related to hospitalization, surgery, rehabilitation, and long-term care reaching billions of dollars annually. For instance, in the United States alone, osteoporosis-related fracture care costs are estimated to exceed $14 billion annually (6), with projections indicating a rise as populations age. In low- and middle-income countries, where access to diagnostic tools like DXA and treatments is limited, the burden is exacerbated by underdiagnosis and undertreatment. The aging global population, particularly in Asia, where countries like China, India, and Vietnam are experiencing rapid demographic shifts, is expected to drive a significant increase in osteoporosis prevalence and fracture incidence in the coming decades, necessitating urgent public health interventions.

In Vietnam, the prevalence of osteoporosis has been extensively studied through the Vietnam Osteoporosis Study (VOS) (7). Our work has provided critical insights into the burden of osteoporosis in the Vietnamese population. A 2011 cross-sectional study involving 357 men and 870 women aged 18 to 89 years found that the prevalence of osteoporosis, defined by T-scores ≤ -2.50 at the femoral neck or lumbar spine, was 29% in postmenopausal women and 10% in men aged 50 and older when using population-specific reference ranges (8). However, when using T-scores based on the US White population (NHANES III), the prevalence was significantly higher, at 44% for women and 30% for men, highlighting the importance of local reference data for accurate diagnosis. A later study in 2021 reported a prevalence of 27% in women and 13% in men aged 50 and older, with 49% of women and 35% of men meeting the US National Osteoporosis Foundation criteria for treatment due to osteoporosis, osteopenia, or prior fracture history (9). The VOS also documented a 12.2% prevalence of asymptomatic vertebral fractures in individuals aged 50 and older, increasing to 20% in those over 70 (10). These findings underscore the significant burden of osteoporosis in Vietnam, particularly among postmenopausal women, and the need for improved screening and prevention strategies, especially as the country's population continues to age rapidly.

The burden of fractures extends beyond the individual patient. The economic impact on the healthcare system is considerable, due to costs related to acute hospitalization, surgery, rehabilitation, long-term care, and productivity losses. Despite this, awareness of osteoporosis among patients and healthcare providers remains limited in many communities in Vietnam, and treatment rates following a first fracture are still unacceptably low—a phenomenon known as the "osteoporosis treatment gap."

2. CURRENT STANDARDS IN OSTEOPOROSIS TREATMENT

For the past three decades, bisphosphonates have been the mainstay of pharmacologic therapy for osteoporosis worldwide. These drugs, which include alendronate, risedronate, ibandronate, and zoledronic acid, act by binding to hydroxyapatite in bone and inhibiting the activity and survival of osteoclasts, the cells responsible for bone resorption.

The antifracture efficacy of bisphosphonates is well-established (11). Large randomized controlled trials have shown that oral alendronate reduces the risk of vertebral fractures by up to 50% and hip fractures by 40–50% (12) in postmenopausal women with osteoporosis (11). Zoledronic acid, given intravenously once yearly, offers similar benefits and has been widely adopted (13), particularly for patients who cannot tolerate oral bisphosphonates or have adherence difficulties.

However, despite their effectiveness, bisphosphonates have certain limitations. Gastrointestinal side effects, such as esophageal irritation and dyspepsia, are common barriers to adherence with oral formulations. Proper administration requires patients to take the medication while fasting, remain upright for at least 30–60 minutes, and avoid eating or drinking during this period. These requirements can be burdensome, especially for elderly patients. Intravenous bisphosphonates, while convenient in terms of dosing frequency, require access to infusion services, which may not be uniformly available across Vietnam, particularly in rural areas.

Another consideration is the concern over long-term safety. Rare but serious adverse events, such as atypical femoral fractures and osteonecrosis of the jaw, have been associated with prolonged bisphosphonate use, although the absolute risk remains very low. These concerns have prompted both patients and clinicians to seek alternative treatment options, particularly for long-term management.

3. ADVANCES IN BONE BIOLOGY: THE RANK/RANKL/OPG PATHWAY

Biologically, osteoporosis arises from an imbalance between bone formation and bone resorption, disrupting the skeletal remodeling process. Osteoblasts, responsible for synthesizing new bone matrix, and osteoclasts, which break down bone tissue, normally maintain equilibrium to ensure bone health. Osteocytes, embedded within the bone matrix, act as mechanosensors, orchestrating this balance by signaling to osteoblasts and osteoclasts via pathways like RANK/RANKL/OPG (14). In osteoporosis, excessive osteoclast activity, often driven by an elevated RANKL/OPG ratio, accelerates bone resorption, outpacing the bone-forming capacity of osteoblasts. This leads to reduced bone mineral density and structural deterioration, increasing fracture risk. Osteocytes also contribute by responding to mechanical stress and hormonal changes, which, when dysregulated, exacerbate the imbalance, further weakening the skeleton.

Over the past three decases, the discovery and characterization of the RANK/RANKL/OPG pathway have been pivotal in elucidating the molecular mechanisms governing bone remodeling, providing critical insights into the pathophysiology of osteoporosis and other bone-related disorders. This pathway has also become a cornerstone for the development of targeted therapeutic interventions that modulate bone resorption.

The RANK/RANKL/OPG pathway involves three key components (15): Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL), its receptor RANK, and Osteoprotegerin (OPG). RANKL, a cytokine belonging to the tumor necrosis factor (TNF) superfamily, is primarily expressed by osteoblasts, bone marrow stromal cells, and activated T cells. It binds to RANK, a receptor found on the surface of osteoclast precursors and mature osteoclasts. This interaction activates intracellular signaling cascades, including the nuclear factor kappa-B (NF-κB) and mitogen-activated protein kinase (MAPK) pathways, which promote osteoclast differentiation, activation, and survival. Consequently, RANKL drives bone resorption by enhancing osteoclastogenesis. OPG, also produced by osteoblasts and stromal cells, acts as a soluble decoy receptor that binds RANKL with high affinity, preventing its interaction with RANK. By inhibiting RANKL-RANK signaling, OPG suppresses osteoclast formation and activity, thereby

reducing bone resorption. The balance between RANKL and OPG is critical in regulating bone homeostasis, with an elevated RANKL/OPG ratio favoring bone loss, as seen in conditions like osteoporosis, rheumatoid arthritis, and metastatic bone disease, while a higher OPG/RANKL ratio promotes bone preservation.

Dysregulation of the RANK/RANKL/OPG pathway is implicated in numerous skeletal disorders. In postmenopausal osteoporosis, estrogen deficiency increases RANKL expression and decreases OPG production, leading to excessive osteoclast activity and accelerated bone loss. Similar mechanisms contribute to bone destruction in inflammatory conditions, such as rheumatoid arthritis, where pro-inflammatory cytokines like TNF-α and interleukin-1 upregulate RANKL expression. In metastatic bone disease, tumor cells often secrete RANKL or induce its production in the bone microenvironment, promoting osteolytic lesions. Conversely, conditions associated with excessive OPG production, such as certain genetic mutations, can lead to osteopetrosis, characterized by overly dense bones due to impaired osteoclast function.

4. DENOSUMAB: MECHANISM OF ACTION AND PHARMACOLOGY

The elucidation of RANK/RANKL/OPG pathway has revolutionized therapeutic approaches to osteoporosis and related conditions. Denosumab, a fully human monoclonal antibody that binds and neutralizes RANKL, mimics the inhibitory effects of OPG, significantly reducing osteoclast activity and bone resorption (16). By binding to RANKL, Denosumab prevents its interaction with the RANK receptor on osteoclast precursors and mature osteoclasts, thereby inhibiting osteoclast differentiation, activation, and survival. This suppression of osteoclast-mediated bone resorption leads to a significant reduction in bone turnover, resulting in increased bone mineral density (BMD) and a decreased risk of fractures.

Unlike bisphosphonates, which are incorporated into the bone matrix and inhibit osteoclast activity through direct cellular toxicity, Denosumab does not bind to bone tissue (17). Bisphosphonates, such as alendronate or zoledronic acid, remain in the bone for years, providing a persistent effect even after discontinuation, which can lead to prolonged suppression of bone turnover. In contrast, Denosumab's effects are fully reversible upon cessation, as its action depends on the presence of the antibody in the circulation. This reversibility is a double-edged sword: while it allows for flexibility in treatment, discontinuation without transitioning to another antiresorptive therapy can lead to a rapid rebound in bone turnover, potentially increasing fracture risk. Studies have shown that after stopping Denosumab, bone turnover markers return to baseline within 12 months, and BMD gains may be lost within 12–24 months, emphasizing the importance of continuous administration or a structured transition plan.

Denosumab is administered as a 60 mg subcutaneous injection every six months, a dosing schedule that enhances patient adherence compared to daily or weekly oral bisphosphonates, which often require strict administration protocols (e.g., fasting and upright posture). The convenience of biannual injections is particularly beneficial for elderly patients or those with polypharmacy, who may struggle with oral medication regimens. The drug's pharmacokinetics further distinguish it from bisphosphonates. As a monoclonal antibody, Denosumab is cleared through the reticuloendothelial system via non-specific IgG catabolism, rather than renal excretion, making it suitable for patients with moderate to severe renal impairment (creatinine clearance <30 mL/min). However, this population requires careful monitoring for hypocalcemia, a potential side effect due to reduced bone resorption and decreased calcium release from bone. Pre-treatment correction of hypocalcemia and adequate calcium and vitamin D supplementation are critical to mitigate this risk, particularly in patients with compromised renal function.

The pharmacodynamic profile of Denosumab is characterized by a rapid onset of action, with significant reductions in bone turnover markers (e.g., C-terminal telopeptide of type 1 collagen) observed within days of administration, and a sustained effect over the six-month dosing interval. This rapid and potent suppression of osteoclast activity contributes to its efficacy but also necessitates vigilance for rare adverse effects, such as osteonecrosis of the jaw (ONJ) and atypical femoral fractures, which have been reported in approximately 0.1–0.3% and <0.1% of patients, respectively, in long-term studies.

Additionally, because RANKL plays a role in immune regulation, there is a theoretical risk of immune suppression, though clinical trials have not shown a significant increase in infections with Denosumab use compared to placebo. The drug's versatility extends beyond osteoporosis to include treatment of bone loss in patients undergoing androgen deprivation therapy for prostate cancer or aromatase inhibitor therapy for breast cancer, as well as prevention of skeletal-related events in patients with bone metastases from solid tumors.

5. THE FREEDOM TRIAL

The clinical efficacy of Denosumab in reducing fracture risk was established through the landmark FREEDOM trial (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every Six Months) (17), a pivotal phase 3, randomized, double-blind, placebo-controlled study. Conducted across 214 centers in 32 countries, including Asian populations, this trial enrolled 7,868 postmenopausal women aged 60–90 years with a T-score between -2.5 and -4.0 at the lumbar spine or total hip. Participants were randomized to receive either Denosumab 60 mg subcutaneously every six months or placebo, with all participants receiving daily calcium (at least 1,000 mg) and vitamin D (at least 400 IU).

The FREEDOM trial demonstrated a 68% relative risk reduction in new vertebral fractures, a 40% reduction in hip fractures, and a 20% reduction in nonvertebral fractures over three years. These findings firmly positioned Denosumab as an effective agent for the prevention of fractures in postmenopausal women with osteoporosis.

Following the initial three-year FREEDOM study, an open-label extension phase followed participants for up to ten years (18), providing valuable insights into the long-term efficacy and safety of Denosumab. The extension data confirmed continued gains in BMD at the lumbar spine and total hip, with cumulative BMD increases of approximately 18% at the lumbar spine and 8% at the total hip over ten years. Importantly, the long-term use of Denosumab was associated with sustained low rates of fractures, and the incidence of adverse events did not increase with prolonged treatment duration.

Comparative studies with bisphosphonates have further enriched the evidence base for Denosumab. In the DECIDE study (19), Denosumab was compared with alendronate in postmenopausal women previously untreated for osteoporosis. After one year, Denosumab was associated with greater increases in BMD at all measured skeletal sites, including the lumbar spine and hip, compared to alendronate. Similar results were observed in the STAND study (20), which evaluated women previously treated with alendronate who switched to Denosumab, confirming superior BMD gains and greater suppression of bone turnover markers with Denosumab.

These pivotal trials and extension studies collectively establish Denosumab as a highly effective agent for reducing fracture risk and increasing BMD in postmenopausal osteoporosis, with a robust safety profile, positioning it as a compelling alternative to bisphosphonates, particularly in specific patient populations.

6. REAL-WORLD EVIDENCE

While RCTs are the gold standard for assessing drug efficacy, real-world evidence (RWE) is critical for understanding the effectiveness, safety, and adherence patterns of medications in routine clinical practice. Several observational studies and registry data have confirmed that Denosumab's benefits observed in clinical trials are reproducible in real-world settings.

Data from the Canadian Database for Osteoporosis and Osteopenia (CANDOO) demonstrated that Denosumab treatment in routine practice led to significant increases in BMD and reductions in fracture incidence similar to those seen in clinical trials (21). Furthermore, studies in European cohorts (22), including elderly patients with multiple comorbidities, have shown that Denosumab maintains its efficacy in increasing BMD and reducing fractures while being well-tolerated across diverse patient populations.

In Japan (23) and South Korea (24), where Denosumab has been used extensively,

real-world studies have shown high treatment persistence rates due to its biannual dosing and minimal gastrointestinal side effects, addressing a common limitation of bisphosphonate therapy. Improved adherence directly correlates with greater reductions in fracture risk, underlining the practical benefits of Denosumab in real-world management of osteoporosis.

7. SAFETY PROFILE, SIDE EFFECTS, AND MANAGEMENT

Denosumab is generally well-tolerated, with a safety profile comparable to placebo in most categories, as evidenced by the FREEDOM trial (17) and its extension (18). However, Denosumab carries risks, including hypocalcemia, especially in patients with vitamin D deficiency, malabsorption, or severe renal impairment (CrCl <30 mL/min). It suppresses bone resorption, potentially lowering serum calcium. In the FREEDOM trial, hypocalcemia was rare (<0.1%) but higher in at-risk groups. Pre-treatment checks of calcium, vitamin D, and renal function are essential, with correction (800–1,000 IU/day vitamin D, 1,000–1,200 mg/day calcium) before starting. Monitor calcium within two weeks post-injection and periodically, especially in renal impairment.

Infections, like cellulitis, are slightly increased (4.1% vs. 3.4% placebo in FREEDOM), possibly due to RANKL's immune role. Patients should report signs of infection (redness, swelling, fever) for prompt antibiotic treatment. Dermatologic reactions (rashes, eczema) occur in 10.8% vs. 8.2% placebo, usually mild and treatable with topical therapies.

Osteonecrosis of the jaw (ONJ) is rare (0.1–0.3% in osteoporosis patients), linked to poor oral hygiene or dental procedures. Pre-treatment dental evaluation and good oral hygiene reduce risk. Atypical femoral fractures (AFF) are also rare (<0.1%), signaled by thigh/groin pain, requiring radiographic evaluation. Prolonged use may increase microdamage, so reassess therapy after 5–10 years.

Discontinuing Denosumab risks rapid bone loss and vertebral fractures (3–6% increased risk). Transition to bisphosphonates post-cessation to mitigate. Musculoskeletal pain (~20%) is common but mild. No significant increase in opportunistic infections is noted.

Overall, Denosumab's safety profile is favorable, with most adverse events being rare or manageable. However, careful patient selection, pre-treatment optimization, ongoing monitoring, and individualized treatment planning are critical to maximizing benefits while minimizing risks.

8. CONCLUSION

Osteoporosis poses a significant global health challenge, exacerbated by aging populations, particularly in Vietnam, where high prevalence rates signal an urgent need for enhanced screening and intervention. The RANK/RANKL/OPG pathway has transformed our understanding of bone remodeling, enabling targeted therapies like Denosumab, which effectively reduces fracture risk and improves BMD. Its unique mechanism, reversibility, and suitability for renal-impaired patients distinguish it from bisphosphonates, though careful management of discontinuation and side effects is essential. Future research into combination therapies and long-term outcomes promises to further optimize osteoporosis treatment, addressing both bone resorption and formation to improve patient outcomes.

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