International Journal of Innovative Technologies in Social Science

e-ISSN: 2544-9435

Operating Publisher
SciFormat Publishing Inc.
ISNI: 0000 0005 1449 8214

2734 17 Avenue SW,
Calgary, Alberta, T3E0A7,
Canada
+15878858911
editorial-office@sciformat.ca

ARTICLE TITLE	DENOSUMAB IN BONE-RELATED DISORDERS: CURRENT CLINICAL APPLICATIONS AND SAFETY CONSIDERATIONS — A NARRATIVE REVIEW
DOI	https://doi.org/10.31435/ijitss.2(50).2026.5696
RECEIVED	23 March 2026
ACCEPTED	17 June 2026
PUBLISHED	24 June 2026
LICENSE	The article is licensed under a **Creative Commons Attribution 4.0 International License.**

DENOSUMAB IN BONE-RELATED DISORDERS: CURRENT CLINICAL APPLICATIONS AND SAFETY CONSIDERATIONS — A NARRATIVE REVIEW

Weronika Smutkiewicz *(Corresponding Author, Email: weronikasmutkiewicz01@gmail.com)*
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0007-4965-1903

Weronika Teterycz
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0000-7486-458X

Wiktoria Goździejewska
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0007-5302-1883

Łukasz Jaworek
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0007-8117-5644

Gabriela Zimka
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0005-3954-7307

Krystian Bjorgen
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0008-0225-7439

Lilianna Jasińska
University of Warmia and Mazury in Olsztyn, Olsztyn, Poland
ORCID ID: 0009-0006-0819-8922

Magdalena Roman
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0004-1261-180X

Martyna Lipiarz
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0001-3124-9250

Michał Niespodziewański
Cardinal Stefan Wyszyński University in Warsaw, Warsaw, Poland
ORCID ID: 0009-0009-0937-1549

ABSTRACT

Denosumab is a fully human monoclonal antibody directed against the receptor activator of nuclear factor kappa-B ligand (RANKL), a central mediator of osteoclast differentiation, activation, and survival. Denosumab, acting by interfering with the RANKL pathway, provides powerful anti-resorptive activity and serves as an effective treatment modality for numerous conditions associated with bones. This narrative review summarizes the current evidence regarding the mechanism of action, pharmacokinetic and pharmacodynamic properties, clinical applications, and safety profile of denosumab.

Denosumab has demonstrated substantial efficacy in osteoporosis, with significant increases in bone mineral density and reductions in vertebral, non-vertebral, and hip fracture risk. In oncology, it is widely used for the prevention of skeletal-related events in patients with bone metastases and multiple myeloma. It has also emerged as an effective targeted therapy in giant cell tumor of bone.

Despite its broad clinical utility, denosumab therapy is associated with important safety considerations. These include hypocalcemia, osteonecrosis of the jaw, atypical femoral fractures, and the rebound phenomenon following treatment discontinuation. Rebound phenomenon is characterized by rapid bone turnover and increased risk of multiple vertebral fractures. These challenges highlight the importance of careful patient selection, monitoring, and long-term treatment planning.

Denosumab represents a cornerstone therapy in the management of bone-related disorders due to its targeted mechanism and robust clinical efficacy. However, its reversible pharmacological profile necessitates individualized therapeutic strategies to optimize outcomes and minimize long-term risks.

KEYWORDS

Denosumab; RANKL; Osteoporosis; Bone Metastases; Multiple Myeloma; Giant Cell Tumor of Bone; Skeletal-Related Events; Rebound Phenomenon

CITATION

Weronika Smutkiewicz, Weronika Teterycz, Wiktoria Goździejewska, Łukasz Jaworek, Gabriela Zimka, Krystian Bjorgen, Lilianna Jasińska, Magdalena Roman, Martyna Lipiarz, Michał Niespodziewański. (2026) Denosumab in Bone-Related Disorders: Current Clinical Applications and Safety Considerations — A Narrative Review. *International Journal of Innovative Technologies in Social Science*. 2(50). doi: 10.31435/ijitss.2(50).2026.5696

1. Methodology

This article was prepared as a narrative review of the current literature on denosumab in bone-related disorders. A literature search was conducted using PubMed, Scopus, and Google Scholar databases. The search strategy included combinations of the following keywords: “denosumab,” “RANKL,” “osteoporosis,” “bone metastases,” “multiple myeloma,” “giant cell tumor of bone,” “hypocalcemia”, “osteonecrosis of the jaw,” “atypical femoral fracture,” and “rebound phenomenon.”

2. Introduction

Bone-related disorders are major global health challenge. The most common ones include osteoporosis, bone metastases, multiple myeloma and primary bone tumors. These diseases are associated with substantial morbidity. Patients suffer from chronic pain and pathological fractures which significantly reduce their quality of life and increase mortality (Compston et al., 2019; Coleman et al., 2020). For several decades, antiresorptive therapy has been the cornerstone of bone disease treatment. Bisphosphonates have long been the mainstay of the treatment. Although highly effective, bisphosphonates are associated with several limitations. The most common adverse effects of these medications are gastrointestinal intolerance, renal toxicity, and long-term skeletal accumulation. The accumulation of bisphosphonates in bone tissue may lead to the development of atypical femoral fractures and osteonecrosis of the jaw (Russell, 2007; Shane et al., 2014). These limitations have driven the development of more targeted therapies aimed at specific molecular pathways involved in bone remodeling. Denosumab is a fully human monoclonal antibody directed against the receptor activator of nuclear factor kappa-B ligand (RANKL). It was developed based on advances in the understanding of

osteoclast biology and the key role of the RANK/RANKL/osteoprotegerin signaling pathway in bone metabolism (Boyle et al., 2003). Denosumab was first approved by the U.S. Food and Drug Administration in 2010 for the treatment of postmenopausal osteoporosis at high risk of fracture. Currently, it is approved for the treatment of osteoporosis, bone metastases, primary bone tumors, such as giant cell tumor of bone, and multiple myeloma. (Cummings et al., 2009; Stopeck et al., 2010; Chawla et al., 2013).

Unlike traditional antiresorptive agents, denosumab provides targeted and reversible inhibition of bone resorption. Its mechanism of action is based on high-affinity binding to RANKL. It allows precise regulation of osteoclast activity without direct integrating into bone tissue. The absence of skeletal accumulation introduces unique challenges, particularly in relation to treatment discontinuation and long-term management strategies (Hanley et al., 2012; Tsourdi et al., 2021).

Currently, denosumab is an integral part of treatment strategies in both endocrinology and oncology. The aim of this narrative review is to provide an integrated overview of the drug denosumab. Attention is given to its mechanism of action, pharmacokinetic and pharmacodynamic properties, clinical applications, and safety profile.

3. Mechanism of Action of Denosumab

Denosumab is a fully human monoclonal IgG2 antibody that selectively binds to receptor activator of nuclear factor kappa-B ligand (RANKL), a key mediator of osteoclast-mediated bone resorption (Hanley et al., 2012). Bone remodeling is regulated by the RANK/RANKL/osteoprotegerin (OPG) signaling axis. RANKL is expressed by osteoblast-lineage cells and osteocytes. It binds to the RANK receptor on osteoclast precursors and mature osteoclasts, thereby promoting their differentiation, activation, and survival (Boyle et al., 2003, Hanley et al., 2012). OPG acts as a soluble decoy receptor that inhibits this interaction, thereby limiting osteoclastogenesis (Hanley et al., 2012). Denosumab functionally mimics the physiological action of OPG.

The interaction between RANKL and RANK activates intracellular signaling pathways, including nuclear factor kappa-B (NF-κB), c-Fos, and nuclear factor of activated T cells 1 (NFATc1). Those pathways are essential regulators of osteoclast differentiation and resorptive function (Boyle et al., 2003). By neutralizing RANKL, denosumab disrupts these signaling cascades, which also leads to a significant reduction in the number and activity of osteoclast (Hanley et al., 2012). This upstream mechanism distinguishes denosumab from bisphosphonates. Bisphosphonates accumulate in mineralized bones and induce osteoclast apoptosis following uptake during active bone resorption (Russell, 2007). Denosumab does not bind to bone matrix, and its effects are dependent on continued systemic exposure, resulting in a reversible mechanism of action (Tsourdi et al., 2021). In addition, denosumab causes rapid and sustained suppression of bone resorption markers. These markers include serum C-terminal telopeptide of type I collagen (CTX) levels, a decrease in which reflects significant inhibition of osteoclast activity (Hanley et al., 2012).

However, prolonged RANKL inhibition may lead to the accumulation of osteoclast precursors capable of rapid differentiation upon treatment discontinuation (Tsourdi et al., 2021). Osteomorphs are cells derived from osteoclasts that retain the ability to revert to active osteoclasts. This discovery has provided important insight into the dynamic regulation of osteoclast activity during and after RANKL inhibition (McDonald et al., 2021). These mechanisms are believed to contribute to the rebound phenomenon observed after discontinuation of denosumab. It is characterized by a rapid increase in bone turnover and an elevated risk of vertebral fractures (Tsourdi et al.,2021). Clinical evidence suggests that reactivation of osteoclastogenesis may occur before significant changes are detectable in conventional biochemical markers. It indicates a temporally complex biological response to the restoration of RANKL signaling (Tsourdi et al., 2021).

The mechanism of action of denosumab also explains its effectiveness in treating various bone-related disorders. In osteoporosis, inhibition of osteoclast-mediated bone resorption leads to increased bone mineral density and reduced fracture risk (Hanley et al., 2012). In patients with bone metastases, denosumab suppresses tumor-induced osteoclast activation and reduces skeletal-related events (Stopeck et al., 2010). In giant cell tumor of bone, where RANKL overexpression drives the formation of osteoclast-like giant cells, denosumab inhibits osteolysis and contributes to tumor stabilization (Chawla et al.,2013).

Denosumab exerts its therapeutic effects through high-affinity neutralization of RANKL, which leads to the inhibition of osteoclast differentiation, activity, and survival (Hanley et al., 2012). Emerging evidence indicates that its biological effects extend beyond direct osteoclast suppression. They also include modulation of precursor cell dynamics and osteoclast recycling processes. These processes explain both its sustained efficacy during treatment and the rebound in bone turnover following discontinuation of treatment (Tsourdi et al., 2021, McDonald et al.,2021).

4. Pharmacokinetics and Pharmacodynamics of Denosumab

Denosumab exhibits pharmacokinetic properties characteristic of monoclonal antibodies, including slow absorption and prolonged systemic exposure. Following subcutaneous administration, denosumab is absorbed via the lymphatic system. Peak serum concentration (C_max) typically is achieved between 7 and 21 days after injection (Bekker et al., 2004; Hanley et al., 2012). Its absolute bioavailability is approximately 61%, which reflects efficient systemic uptake (Bekker et al., 2004). The terminal elimination half-life ranges from approximately 25 to 32 days. It allows infrequent dosing schedules. For example, the standard treatment regimen for osteoporosis involves administering 60 mg subcutaneously every 6 months (Hanley et al., 2012). Denosumab is not eliminated via renal or hepatic pathways. It undergoes degradation into small peptides and amino acids through the reticuloendothelial system. This mechanism of elimination is typical for IgG antibodies (Hanley et al., 2012). Consequently, dose adjustment is not required in patients with renal impairment. However, these patients are at increased risk of hypocalcemia due to disturbances in calcium homeostasis (Miller et al., 2009).

From a pharmacodynamic perspective, denosumab induces a rapid, dose-dependent suppression of bone resorption. Serum levels of C-terminal telopeptide of type I collagen (CTX) decrease significantly within 24–72 hours following administration. Maximal suppression of CTX is observed within the first month (Eastell et al., 2011). This suppression is sustained throughout the dosing interval. It consists of continued inhibition of osteoclast-mediated bone resorption (Hanley et al., 2012, Bone et al., 2011). The pharmacodynamic response to denosumab is characterized by a temporal dissociation between bone resorption and bone formation. While bone resorption markers decline rapidly, bone formation markers such as procollagen type I N-terminal propeptide (P1NP) decrease more gradually. It results in a transient uncoupling of bone remodeling that contributes to increases in bone mineral density (Eastell et al., 2011).

A key feature of denosumab's pharmacodynamics is the reversibility of its effects. Denosumab does not accumulate in bone tissue, therefore its activity is directly dependent on circulating drug concentrations (Hanley et al., 2012). As serum levels decline following discontinuation, bone turnover markers increase above baseline levels within several months. It reflects rapid reactivation of osteoclast activity (Tsourdi et al., 2021). This rebound in bone turnover has important clinical implications. It is associated with accelerated bone loss and an increased risk of multiple vertebral fractures. This applies primarily to patients who do not receive further antiresorptive therapy after discontinuation (Tsourdi et al., 2021). The magnitude of this rebound effect highlights the importance of treatment continuity and appropriate transition strategies in long-term denosumab therapy (Tsourdi et al., 2021).

Denosumab is characterized by slow absorption, moderate bioavailability, nonlinear pharmacokinetics, and a prolonged elimination half-life. Its pharmacodynamic profile is defined by rapid and long-lasting suppression of bone resorption. Upon discontinuation of treatment, bone turnover reversibly returns to baseline. These pharmacokinetic–pharmacodynamic relationships are critical for understanding both the clinical efficacy and safety profile of denosumab.

5. Clinical Applications of Denosumab

5.1 Osteoporosis

Osteoporosis is a chronic, systemic skeletal disorder defined by low bone mass and microarchitectural deterioration of bone tissue, leading to increased bone fragility and a consequent rise in fracture risk (World Health Organization; Compston et al., 2019). According to the diagnostic criteria established by the World Health Organization, osteoporosis is defined as a bone mineral density (BMD) T-score ≤ -2.5 at the lumbar spine, femoral neck, or total hip (Compston et al., 2019). Osteoporosis represents a major global health burden. It is estimated that over 200 million people worldwide are affected. Approximately one in three women and one in five men over the age of 50 experiencing osteoporotic fractures during their lifetime (Sozen et al., 2017; Kanis et al., 2021). The incidence of osteoporotic fractures is expected to rise significantly due to population aging, particularly in Europe and North America (Kanis et al., 2021). Fragility fractures, especially of the hip and vertebrae, are associated with increased mortality, reduced quality of life, and substantial healthcare costs (Compston et al., 2019).

The pathophysiology of osteoporosis stems primarily from an imbalance between bone resorption and bone formation. Bone resorption predominates, with osteoclasts playing a key role in this process. In postmenopausal osteoporosis, estrogen deficiency plays a central role by promoting the formation of osteoclast and prolonging their survival (Eastell et al., 2016). Dysregulation of the RANK/RANKL/OPG signaling pathway is a key mechanism underlying increased bone resorption in osteoporosis. Enhanced expression of

RANKL and decreased availability of OPG lead to increased activation of osteoclasts, resulting in accelerated bone loss (Boyle et al., 2003). Additional contributing mechanisms include increased production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-α (TNF-α). Osteoblast function also declines with age. (Eastell et al., 2016).

Clinical trials have shown that denosumab significantly increases BMD at major skeletal sites. In the pivotal FREEDOM trial, three years of treatment with denosumab resulted in increase in BMD of approximately 9% at the lumbar spine and 6% at the total hip (Cummings et al., 2009). Long-term extension studies have shown that continued therapy leads to progressive increases in BMD for up to 10 years. (Bone et al., 2017). Denosumab also significantly reduces fracture risk. In postmenopausal women with osteoporosis, it has been associated with a 68% reduction in vertebral fractures, a 40% reduction in hip fractures, and a 20% reduction in non-vertebral fractures (Cummings et al., 2009). Denosumab is administered as a 60 mg subcutaneous injection every six months, offering a convenient dosing regimen. This treatment regimen may promote better adherence to treatment recommendations compared with oral bisphosphonates.

However, the main limitation of denosumab therapy is the reversibility of its effects. Discontinuation of treatment is associated with a rapid increase in bone turnover, significant loss of BMD, and an increased risk of multiple vertebral fractures (Tsourdi et al., 2021). This rebound phenomenon is believed to result from the reactivation of suppressed osteoclast precursors and increased RANKL activity following drug discontinuation (Anastasilakis et al., 2021). Consequently, current clinical guidelines recommend the initiation of sequential antiresorptive therapy. Typically, bisphosphonates are initiated in patients to prevent this phenomenon (Tsourdi et al., 2021).

5.2 Bone Metastases

Bone metastases are a common complication of advanced malignant tumors, particularly in cancers such as breast cancer, prostate cancer, and lung cancer. It is estimated that up to 70% of patients with advanced breast or prostate cancer develop skeletal metastases (Coleman et al., 2020). These metastases are associated with significant morbidity, including bone pain, pathological fractures, spinal cord compression, and tumor-inducted hypercalcemia—collectively referred to as skeletal-related events (SREs) (Coleman, 2006). The pathophysiology of bone metastases is characterized by a complex interaction between tumor cells and the bone microenvironment. Tumor cells secrete factors such as parathyroid hormone-related peptide (PTHrP), interleukins, and prostaglandins, which stimulate osteoblasts to increase RANKL expression. It promotes the differentiation and activation of osteoclast, leading to increased bone resorption (Weilbaecher et al., 2011). The release of growth factors from the bone matrix, including transforming growth factor-β (TGF-β), further enhances tumor proliferation. This creates a self-perpetuating “vicious cycle” of bone destruction and tumor growth (Coleman et al., 2020). Clinical trials have shown that denosumab is highly effective in reducing the risk of SREs in patients with bone metastases. In a pivotal phase III trial involving patients with metastatic castration-resistant prostate cancer, denosumab delayed the time to the first SRE compared with zoledronic acid (median 20.7 vs 17.1 months) (Fizazi et al., 2011). Similar results were observed in patients with breast cancer, where denosumab demonstrated superior efficacy compared with zoledronic acid in preventing SREs (Stopeck et al., 2010). Denosumab is typically administered at a dose of 120 mg subcutaneously every four weeks to prevent SREs in patients with bone metastases. It does not accumulate in bone matrix and exerts its effects through continuous, systemic inhibition of RANKL. As a result, its pharmacological effect is reversible. Discontinuation of the drug may lead to increased bone turnover. The clinical consequences of this phenomenon in oncology populations are less clearly defined than in the case of osteoporosis (Coleman et al., 2020). Recent studies have also examined the potential role of denosumab beyond the prevention of SREs. Emerging evidence suggests that inhibition of the RANKL pathway may have direct or indirect effects on tumor progression and the immune microenvironment. However, these findings are still under investigation remain and have not yet translated into clear clinical benefits in terms of overall survival (Ahern et al., 2018).

5.3 Multiple Myeloma

Multiple myeloma (MM) is a malignant plasma cell disorder characterized by clonal proliferation of plasma cells in the bone marrow. MM leads to extensive skeletal destruction, bone pain, anemia, renal impairment, and immunodeficiency (Rajkumar, 2020). It accounts for approximately 10% of all hematologic malignancies and remains the second most common blood cancer worldwide (Kazandjian, 2016). The global incidence of multiple myeloma is estimated at approximately 1.7 cases per 100,000 individuals per year, with higher rates observed in older populations and males (Cowan et al., 2018). The median age at diagnosis is

around 65–70 years, and the disease burden is expected to increase due to population aging (Rajkumar, 2020). Despite advances in therapy, multiple myeloma remains an incurable disease, with skeletal-related complications representing a major source of morbidity (Terpos et al., 2021).

Bone disease is a hallmark feature of multiple myeloma and occurs in up to 80–90% of patients during the disease (Terpos et al., 2021). The pathophysiology of myeloma-related bone disease is characterized by a profound imbalance between osteoclast-mediated bone resorption and osteoblast-mediated bone formation. This imbalance results in purely osteolytic lesions without compensatory bone formation (Roodman, 2010). Malignant plasma cells interact with the bone marrow microenvironment to promote osteoclastogenesis. Myeloma cells stimulate stromal cells and osteoblasts to increase the expression of RANKL, while simultaneously suppressing OPG. Consequently, it enhances osteoclast differentiation and activity (Terpos et al., 2021; Roodman, 2010). In addition, myeloma cells secrete various cytokines, including interleukin-6 (IL-6), macrophage inflammatory protein-1α (MIP-1α), and tumor necrosis factor-α (TNF-α), which further promote osteoclast activation and bone resorption (Roodman, 2010). Concurrently, osteoblast function is markedly inhibited through the secretion of Wnt signaling antagonists such as Dickkopf-1 (DKK1) and sclerostin, leading to suppression of bone formation (Terpos et al., 2021). This dual mechanism—enhanced bone resorption and impaired bone formation—results in progressive skeletal destruction and increased risk of pathological fractures.

The efficacy of denosumab in MM was demonstrated in a large, randomized phase III trial comparing denosumab with zoledronic acid in patients with newly diagnosed MM. The study showed that denosumab was non-inferior to zoledronic acid in delaying the time to first SRE (Raje et al., 2018). Notably, denosumab was associated with improved progression-free survival in certain subgroups, although no significant difference in overall survival was observed (Raje et al., 2018). An important advantage of denosumab over zoledronic acid in multiple myeloma is its lack of renal toxicity. Zoledronic acid requires dose adjustment and careful monitoring in patients with renal impairment, which is common in MM. Denosumab is not renally cleared and can be safely used in this population (Terpos et al., 2021). It makes denosumab particularly valuable in patients with compromised kidney function.

Denosumab is administered at a dose of 120 mg subcutaneously every four weeks for the prevention of SREs in patients with MM. Clinical studies have shown that it effectively reduces the incidence of skeletal complications, including pathological fractures and the need for radiation or surgery to bone (Raje et al., 2018).

Current clinical guidelines recommend the use of bone-targeted agents, including denosumab or bisphosphonates, in all patients with active MM and evidence of bone disease (Terpos et al., 2021). The choice between these agents should be individualized based on patient characteristics, particularly renal function and risk of adverse events.

5.4 Giant Cell Tumor of Bone

Giant cell tumor of bone (GCTB) is a primary bone neoplasm classified as an intermediate, locally aggressive tumor with a low but present metastatic potential. It accounts for approximately 4–5% of all primary bone tumors and typically occurs in young adults between 20 and 40 years of age, with a slight predominance in women (Parmeggiani et al., 2021). GCTB most commonly arises in the meta-epiphyseal regions of long bones, particularly the distal femur, proximal tibia, and distal radius. Radiographically, GCTB is characterized by osteolytic lesions with cortical destruction (Parmeggiani et al., 2021).

GCTB is composed of three main cellular components: neoplastic stromal cells, mononuclear histiocytic cells, and multinucleated osteoclast-like giant cells. The stromal cells represent the true neoplastic component of the tumor, whereas the giant cells are reactive and derived from the monocyte–macrophage lineage (Yamamoto et al., 2020). The tumor exhibits aggressive local behavior, with a high rate of recurrence following surgical treatment. In rare cases, the tumor metastasizes, most commonly to the lungs (Parmeggiani et al., 2021).

The pathophysiology of GCTB is strongly driven by dysregulation of the RANK/RANKL signaling pathway. Neoplastic stromal cells overexpress receptor activator of RANKL, which promotes the recruitment, differentiation, and activation of osteoclast precursors into multinucleated osteoclast-like giant cells (López-Pousa et al., 2015). These giant cells are responsible for extensive osteolysis through the secretion of proteolytic enzymes and acidification of the bone microenvironment, leading to progressive bone destruction (Parmeggiani et al., 2021). GCTB is characterized in over 90% of cases by mutations in the H3F3A gene, particularly the G34W substitution, which plays a key role in tumorigenesis and epigenetic dysregulation (Yamamoto et al., 2020; Hasenfratz et al., 2021). These mutations contribute to abnormal stromal cell behavior

and enhanced RANKL expression, further amplifying osteoclastogenesis and bone resorption (López-Pousa et al., 2015).

Given the central role of RANKL in the pathogenesis of GCTB, denosumab has emerged as a highly effective targeted therapy. Denosumab induces significant tumor response, leading to a marked reduction in osteoclast-like giant cells and promoting new bone formation within the lesion, resulting in structural stabilization (Chawla et al., 2013; Li et al., 2020). In many cases, denosumab facilitates surgical downstaging, allowing for less extensive and function-preserving procedures (Chawla et al., 2013).

Denosumab is particularly indicated in patients with unresectable tumors, tumors located in anatomically challenging sites (e.g., spine or pelvis), or cases where surgery would result in significant morbidity. In such settings, it may be used as primary therapy or as neoadjuvant treatment prior to surgery (Chawla et al., 2013; Li et al., 2020). In advanced or metastatic GCTB, long-term or even continuous administration may be required to maintain disease control (Li et al., 2020). Despite its efficacy, denosumab therapy is associated with certain limitations. Tumor recurrence has been reported after discontinuation of treatment, likely due to persistence of neoplastic stromal cells that are not directly targeted by the drug (Li et al., 2020). Additionally, long-term use may be associated with adverse effects such as osteonecrosis of the jaw and hypocalcemia, necessitating careful patient monitoring (Li et al., 2020).Studies have also highlighted that denosumab induces significant histological changes in GCTB, including depletion of giant cells and increased bone matrix deposition, which may complicate pathological assessment and differentiation from other bone lesions (Chawla et al., 2013).

6. Safety and Adverse Effects of Denosumab

6.1 Hypocalcemia

Hypocalcemia is a well-recognized and mechanistically predictable adverse effect of denosumab therapy, resulting directly from potent inhibition of osteoclast-mediated bone resorption. Osteoclast activity contributes to the maintenance of extracellular calcium homeostasis by releasing calcium from the bone matrix. Denosumab, through high-affinity binding to RANKL, suppresses osteoclast differentiation and function, thereby markedly reducing calcium efflux from bone into the circulation (Block et al., 2012; Bone et al., 2011). This disruption of calcium homeostasis is particularly clinically relevant in patients with impaired compensatory mechanisms. In healthy individuals, reductions in serum calcium are counterbalanced by increased secretion of parathyroid hormone (PTH), which enhances renal calcium reabsorption, stimulates conversion of 25-hydroxyvitamin D to its active form (1,25-dihydroxyvitamin D), and promotes intestinal calcium absorption. However, in patients with chronic kidney disease, vitamin D deficiency, or hypoparathyroidism, these adaptive responses are blunted, significantly increasing the risk of severe hypocalcemia during denosumab therapy (Block et al., 2012; Dave et al., 2015). Denosumab-induced hypocalcemia reflects a state of reduced skeletal calcium mobilization combined with ongoing peripheral calcium utilization. This is particularly evident in conditions characterized by high baseline bone turnover, such as metastatic bone disease or multiple myeloma, where abrupt suppression of osteoclast activity leads to a rapid decline in serum calcium levels (Body et al., 2018). Additionally, decreased bone resorption limits the availability of calcium necessary for maintaining neuromuscular and cardiovascular stability. Hypocalcemia may range from asymptomatic biochemical abnormalities to severe, life-threatening manifestations. Mild hypocalcemia is often detected incidentally through laboratory monitoring. Moderate to severe hypocalcemia may present neuromuscular irritability, including perioral numbness, paresthesia, muscle cramps, carpopedal spasm, and tetany. In more advanced cases, hypocalcemia can lead to seizures, laryngospasm, and cardiac complications such as QT interval prolongation and ventricular arrhythmias (Dave et al., 2015). The incidence and severity of hypocalcemia are dose-dependent and vary according to the clinical indication. Higher rates are observed in oncology patients receiving denosumab at 120 mg every 4 weeks compared to patients treated for osteoporosis at 60 mg every 6 months (Body et al., 2018). Moreover, the risk is greatest during the initial weeks following treatment initiation, corresponding to the period of maximal suppression of bone resorption (Block et al., 2012). Preventive strategies are essential to minimize the risk of hypocalcemia. These include assessment and correction of vitamin D deficiency prior to initiation of therapy, adequate calcium and vitamin D supplementation, and close monitoring of serum calcium levels, particularly in high-risk populations. In patients with renal impairment, more frequent monitoring is recommended due to impaired activation of vitamin D and reduced renal calcium reabsorption (Dave et al., 2015). Management of denosumab-induced hypocalcemia depends on severity. Mild cases may be managed with oral calcium and vitamin D supplementation. Severe hypocalcemia requires intravenous calcium administration and, in some cases, active vitamin D analogues such as calcitriol. Temporary interruption of denosumab therapy may be necessary in refractory cases (Body et al., 2018).

6.2 Osteonecrosis of the Jaw

Medication-related osteonecrosis of the jaw (MRONJ) is a rare but clinically significant adverse effect associated with antiresorptive therapies, including denosumab. It is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula, persisting for more than 8 weeks in patients with current or prior exposure to antiresorptive agents and no history of radiation therapy to the craniofacial region (Ruggiero et al., 2022). The incidence of MRONJ varies depending on the indication and dosing regimen of denosumab. In patients treated for osteoporosis (60 mg every 6 months), the risk remains very low, estimated at approximately 0.001–0.01% per year. In oncology patients receiving high-dose therapy (120 mg every 4 weeks), the incidence increases substantially, reaching approximately 1–2% and rising with longer duration of treatment (Bone et al., 2017; Saad et al., 2012; Ruggiero et al., 2022). The pathogenesis of MRONJ is multifactorial and reflects the interplay between suppressed bone remodeling, local microenvironmental factors, and infectious processes. Denosumab exerts its effect through potent inhibition of RANKL, leading to profound suppression of osteoclast-mediated bone resorption. While this mechanism is therapeutically beneficial, it also impairs physiological bone turnover, reducing the capacity of bone to repair microdamage and respond to mechanical stress (Ruggiero et al., 2022, Khan et al., 2015). This effect is particularly pronounced in the jawbones, which are characterized by high baseline turnover due to continuous mechanical loading and exposure to the oral microbiome. In this context, inhibition of osteoclast function leads to accumulation of microdamage, impaired remodeling, and eventual bone necrosis. In addition to suppressed bone turnover, impaired angiogenesis has been proposed as a contributing factor in MRONJ. Reduced vascularization may compromise tissue perfusion and delay healing following minor trauma or invasive dental procedures (Khan et al., 2015; Ruggiero et al., 2022). Bacterial colonization of exposed bone plays a critical role in disease progression, with chronic infection and inflammation exacerbating tissue damage and preventing resolution of necrotic lesions (Ruggiero et al., 2022). The development of MRONJ is strongly influenced by a range of local and systemic risk factors. Invasive dental procedures, particularly tooth extractions, represent the most significant precipitating events. Additional risk factors include poor oral hygiene, pre-existing periodontal disease, prolonged duration of antiresorptive therapy, and high dose denosumab used in oncologic settings. Concomitant use of corticosteroids, chemotherapy, or antiangiogenic agents further increases susceptibility, as do comorbid conditions such as diabetes mellitus and smoking (Ruggiero et al., 2022; Khan et al., 2015). Clinically, MRONJ most commonly affects the mandible and typically presents with exposed necrotic bone in the oral cavity. Early stages may be asymptomatic or associated with mild discomfort, but disease progression can lead to significant pain, soft tissue swelling, purulent discharge, and secondary infection. Additional manifestations include loosening of teeth, fistula formation, halitosis, and, in advanced cases, pathological fractures. The clinical course is often chronic and may involve recurrent exacerbations (Ruggiero et al., 2022). Given the limited effectiveness of treatment once MRONJ is established, prevention remains the cornerstone of management. A comprehensive dental evaluation is recommended prior to initiation of denosumab therapy, with completion of all necessary invasive procedures before treatment begins. During therapy, maintenance of optimal oral hygiene and regular dental follow-up are essential. Elective invasive dental procedures should be avoided whenever possible, and when unavoidable, should be performed with careful risk assessment. Patient education regarding early symptoms and the importance of prompt reporting is also critical. In high-risk individuals, a multidisciplinary approach involving oncologists, endocrinologists, and dental specialists is recommended to minimize the risk of MRONJ (Ruggiero et al., 2022).

6.3 Rebound Phenomenon of Discontinuation of Denosumab

Discontinuation of denosumab is associated with a well-documented rebound phenomenon characterized by a rapid increase in bone turnover, accelerated loss of BMD, and a markedly increased risk of multiple vertebral fractures. This phenomenon reflects the reversible nature of denosumab's mechanism of action and represents a unique clinical challenge in long-term management of patients receiving antiresorptive therapy (Tsourdi et al., 2021). The rebound effect is driven by abrupt restoration and overshoot of RANKL signaling following withdrawal of denosumab. During treatment, continuous inhibition of RANKL leads to suppression of osteoclast differentiation and activity but also results in the accumulation of osteoclast precursors within the bone microenvironment. Upon discontinuation, these precursors rapidly differentiate into mature osteoclasts, leading to a transient but pronounced increase in osteoclast-mediated bone resorption (Tsourdi et al., 2021). Discontinuation of denosumab leads to a rapid increase in bone turnover markers, particularly serum C-terminal telopeptide of type I collagen (CTX), which often rises above baseline levels

within a few months. This increase reflects a state of high bone turnover that exceeds pre-treatment activity (Tsourdi et al., 2021). The rebound phenomenon is associated with substantial and rapid loss of BMD, particularly at trabecular-rich sites such as the spine. Studies have shown that BMD gains achieved during denosumab therapy may be largely lost within 12–24 months after discontinuation if no subsequent therapy is initiated (Bone et al., 2017; Tsourdi et al., 2021). More importantly, this period is associated with a significantly increased risk of multiple vertebral fractures, often occurring in clusters and within a relatively short time frame (Cummings et al., 2018; Anastasilakis et al., 2021). The timing of the rebound effect is clinically relevant. Increases in bone turnover markers are typically observed within 3–6 months after the last dose, with peak activity occurring around 6–9 months. The risk of vertebral fractures is highest within the first 12 months following discontinuation, particularly in patients with prior vertebral fractures or prolonged denosumab exposure (Tsourdi et al., 2021). Appropriate discontinuation strategies are essential. Current evidence strongly supports the use of sequential antiresorptive therapy following denosumab withdrawal. Bisphosphonates, particularly zoledronic acid or oral alendronate, are commonly used to mitigate rebound bone loss by inhibiting osteoclast activity and stabilizing bone turnover (Tsourdi et al., 2021; Anastasilakis et al., 2021). The optimal timing of sequential therapy remains an area of ongoing research; however, initiation is generally recommended within 6 months after the last denosumab injection, corresponding to the expected resurgence of bone turnover. Monitoring bone turnover markers may help guide treatment decisions and assess response to therapy (Tsourdi et al., 2021).

6.4 Atypical Femoral Fractures

Atypical femoral fractures (AFF) are rare insufficiency fractures that occur in the subtrochanteric region or femoral shaft. These fractures are characterized by a transverse or short oblique configuration, minimal or no trauma, and specific radiographic features including cortical thickening and a medial spike (Shane et al., 2014). Although AFFs are most associated with long-term bisphosphonate therapy, they have also been reported in patients receiving denosumab, reflecting a shared mechanism related to suppression of bone remodeling (Bone et al., 2017). The pathophysiology of AFF is primarily linked to prolonged inhibition of osteoclast-mediated bone turnover. Denosumab leads to a marked reduction in bone remodeling activity. While this effect is beneficial in reducing pathological bone resorption, sustained suppression of remodeling impairs the repair of microdamage that accumulates in cortical bone under repetitive mechanical stress (Shane et al., 2014). Over time, this results in structural weakening of the femoral cortex and predisposition to stress fractures. Reduced bone turnover leads to accumulation of older, more mineralized bones with decreased toughness and increased brittleness. Inadequate remodeling prevents replacement of microcracks, allowing them to propagate and coalesce into complete fractures. This process is particularly relevant in the femoral shaft, which is subjected to high mechanical loading (Shane et al., 2014). Clinically, AFFs are often preceded by prodromal symptoms, most notably persistent thigh or groin pain, which may occur weeks to months before fracture completion. Bilateral involvement is relatively common, and radiographic evaluation frequently reveals cortical thickening or incomplete fractures on the contralateral side (Shane et al., 2014). The incidence of AFF in patients treated with denosumab is low. Long-term extension studies in osteoporosis populations report very low rates (generally <0.1 per 1,000 patient-years), indicating that this complication is rare compared to the overall fracture prevention benefits of therapy (Bone et al., 2017). However, the risk may increase with prolonged duration of treatment and cumulative suppression of bone turnover. Risk factors for AFF include long-term antiresorptive therapy, advanced age, glucocorticoid use, and underlying metabolic bone disorders. The contribution of denosumab specifically remains less well defined than that of bisphosphonates, but available evidence suggests a similar mechanistic basis (Shane et al., 2014).

6.5 Other Adverse Effects

In addition to the major adverse events described above, denosumab therapy has been associated with several less common and generally mild to moderate adverse effects. These include dermatological, musculoskeletal, and infectious complications, which are typically manageable and rarely necessitate treatment discontinuation.

Dermatological reactions, such as eczema, dermatitis, and rash, have been reported in clinical trials, likely reflecting the role of RANKL in skin immune homeostasis (Cummings et al., 2009; Hanley et al., 2012). Although usually mild, these reactions may occasionally require symptomatic treatment. Musculoskeletal symptoms, including arthralgia, back pain, and limb pain, are among the most frequently reported adverse effects. These are generally transient and of low severity but may affect patient adherence in long-term therapy

(Bone et al., 2017). Denosumab may also influence immune function due to the involvement of RANKL in immune cell regulation, particularly in dendritic cell function and lymph node development. Clinical studies have reported a slightly increased incidence of infections, most notably skin infections such as cellulitis, although the overall risk of serious infections remains low (Cummings et al., 2009; Diker-Cohen et al., 2020). Rare cases of hypersensitivity reactions, including urticaria and, very rarely, anaphylaxis, have also been described. These events are uncommon but warrant immediate discontinuation of therapy if they occur (Bone et al., 2017).

7. Discussion

Denosumab represents a major advancement in the management of bone-related disorders due to its targeted mechanism of action and potent anti-resorptive effects. By selectively inhibiting RANKL, it effectively suppresses osteoclast-mediated bone resorption, translating into significant clinical benefits across multiple indications, including osteoporosis, metastatic bone disease, multiple myeloma and giant cell tumor of bone (Kendler et al., 2022; Chawla et al., 2013). Compared with bisphosphonates, denosumab offers a distinct pharmacological profile, characterized by the absence of skeletal accumulation and a more rapid and profound suppression of bone turnover (Cummings et al., 2009; Ferrari et al., 2015).

One of the key advantages of denosumab is its consistent efficacy in increasing BMD and reducing fracture risk, particularly in patients at high risk of osteoporotic fractures (Cummings et al., 2009; Kendler et al., 2022). In oncology settings, denosumab has demonstrated superiority or non-inferiority to zoledronic acid in preventing skeletal-related events, highlighting its clinical relevance in patients with bone metastases (Stopeck et al., 2010; Fizazi et al., 2011). Furthermore, its role in the management of giant cell tumor of bone underscores the importance of RANKL signaling in tumor-associated osteolysis and provides a targeted therapeutic approach for this rare but locally aggressive condition (Chawla et al., 2013).

Despite these benefits, several important limitations and clinical challenges remain. A defining feature of denosumab therapy is the reversibility of its pharmacodynamic effects, which distinguishes it from bisphosphonates but also introduces significant risks following treatment discontinuation. The rebound phenomenon, characterized by a rapid increase in bone turnover and an elevated risk of multiple vertebral fractures, has emerged as a major concern in long-term management (Tsourdi et al., 2021; Cummings et al., 2018). This effect is thought to be driven by the accumulation of osteoclast precursors and alterations in bone cellular dynamics during RANKL inhibition, leading to exaggerated osteoclast activity upon withdrawal (McDonald et al., 2021).

Another critical issue is the optimal duration of therapy and the management of treatment discontinuation. Currently, there is no universally accepted strategy for safely stopping denosumab, although sequential therapy with bisphosphonates has been proposed to mitigate rebound-associated bone loss (Tsourdi et al., 2021). However, the effectiveness of such strategies may vary depending on patient characteristics, duration of prior treatment, and timing of transition, highlighting the need for individualized treatment approaches.

Safety considerations also play a central role in clinical decision-making. Although denosumab is generally well tolerated, it has been associated with adverse effects such as hypocalcemia, osteonecrosis of the jaw, and atypical femoral fractures, particularly with long-term use (Cummings et al., 2009; Bone et al., 2017). These risks necessitate careful patient selection, monitoring of calcium levels, and appropriate preventive measures, especially in high-risk populations.

Long-term data on denosumab use beyond 10 years are limited, and the effects of prolonged suppression of bone remodeling on bone quality and microarchitecture are not fully understood. Additionally, the identification of biomarkers that could predict response to therapy or risk of rebound remains an area of ongoing research. Further studies are needed to optimize treatment duration, define safe discontinuation protocols, and better understand interindividual variability in response to denosumab.

Denosumab is a highly effective antiresorptive agent with broad clinical applications in bone-related diseases. Its targeted mechanism and potent pharmacodynamic effects offer significant therapeutic advantages; however, its reversible mode of action introduces unique challenges, particularly in the context of treatment discontinuation. A deeper understanding of the underlying biological mechanisms, combined with individualized clinical strategies, is essential to maximize benefits while minimizing risks associated with denosumab therapy.

8. Conclusions

Denosumab is an incredibly powerful targeted drug that has revolutionized the treatment of bone diseases due to its ability to inhibit the osteoclastic action stimulated by RANKL. It has proven to be effective for improving BMD and preventing bone disorders and complications. Nevertheless, due to its pharmacological reversibility, denosumab poses several issues that can arise when using it. The potential for rebound bone loss and vertebral fractures after stopping denosumab treatment are among the most concerning problems with this therapy. In the future, more research should be conducted to find ways to optimize the course and duration of treatment with this medication.

REFERENCES

1. Ahern, E., Smyth, M. J., Dougall, W. C., & Teng, M. W. L. (2018). Roles of the RANKL–RANK axis in antitumour immunity: Implications for therapy. *Nature Reviews Clinical Oncology, 15*(11), 676–693. https://doi.org/10.1038/s41571-018-0095-y
2. Anastasilakis, A. D., Polyzos, S. A., & Makras, P. (2021). Denosumab discontinuation and the rebound phenomenon: A narrative review. *Journal of Clinical Medicine, 10*(1), 152. https://doi.org/10.3390/jcm10010152
3. Bekker, P. J., Holloway, D. L., Rasmussen, A. S., et al. (2004). A single-dose placebo-controlled study of AMG 162, a fully human monoclonal antibody to RANKL, in postmenopausal women. *Journal of Bone and Mineral Research, 19*(7), 1059–1066. https://doi.org/10.1359/jbmr.040305
4. Block, G. A., Bone, H. G., Fang, L., et al. (2012). A single-dose study of denosumab in patients with various degrees of renal impairment. *Journal of Bone and Mineral Research, 27*(7), 1471–1479. https://doi.org/10.1002/jbmr.1613
5. Body, J. J., von Moos, R., Niepel, D., & Tombal, B. (2018). Hypocalcaemia in patients with prostate cancer treated with a bisphosphonate or denosumab: Prevention supports treatment completion. *BMC Urology, 18*, 81. https://doi.org/10.1186/s12894-018-0393-9
6. Bone, H. G., Bolognese, M. A., Yuen, C. K., et al. (2011). Effects of denosumab treatment and discontinuation on bone mineral density and bone turnover markers in postmenopausal women with low bone mass. *Journal of Clinical Endocrinology & Metabolism, 96*(4), 972–980. https://doi.org/10.1210/jc.2010-1502
7. Bone, H. G., Wagman, R. B., Brandi, M. L., et al. (2017). 10 years of denosumab treatment in postmenopausal women with osteoporosis: Results from the phase 3 randomised FREEDOM trial and open-label extension. *The Lancet Diabetes & Endocrinology, 5*(7), 513–523. https://doi.org/10.1016/S2213-8587(17)30138-9
8. Boyle, W. J., Simonet, W. S., & Lacey, D. L. (2003). Osteoclast differentiation and activation. *Nature, 423*, 337–342. https://doi.org/10.1038/nature01658
9. Chawla, S., Henshaw, R., Seeger, L., et al. (2013). Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: Interim analysis of an open-label, parallel-group, phase 2 study. *The Lancet Oncology, 14*(9), 901–908. https://doi.org/10.1016/S1470-2045(13)70277-8
10. Coleman, R., Hadji, P., Body, J. J., et al. (2020). Bone health in cancer: ESMO clinical practice guidelines. *Annals of Oncology, 31*(12), 1650–1663. https://doi.org/10.1016/j.annonc.2020.07.019
11. Coleman, R. E. (2006). Clinical features of metastatic bone disease and risk of skeletal morbidity. *Clinical Cancer Research, 12*(20), 6243s–6249s. https://doi.org/10.1158/1078-0432.CCR-06-0931
12. Compston, J., McClung, M. R., & Leslie, W. D. (2019). Osteoporosis. *The Lancet, 393*(10169), 364–376. https://doi.org/10.1016/S0140-6736(18)32112-3
13. Cowan, A. J., Allen, C., Barac, A., et al. (2018). Global burden of multiple myeloma: A systematic analysis for the Global Burden of Disease Study 2016. *JAMA Oncology, 4*(9), 1221–1227. https://doi.org/10.1001/jamaoncol.2018.2128
14. Cummings, S. R., Ferrari, S., Eastell, R., et al. (2018). Vertebral fractures after discontinuation of denosumab: A post hoc analysis of the randomized placebo-controlled FREEDOM trial and its extension. *Journal of Bone and Mineral Research, 33*(2), 190–198. https://doi.org/10.1002/jbmr.3337
15. Cummings, S. R., San Martin, J., McClung, M. R., et al. (2009). Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *New England Journal of Medicine, 361*, 756–765. https://doi.org/10.1056/NEJMoa0809493
16. Dave, V., Chiang, C. Y., Booth, J., & Mount, P. F. (2015). Hypocalcemia post denosumab in patients with chronic kidney disease stage 4–5. *American Journal of Nephrology, 41*(2), 129–137. https://doi.org/10.1159/000380960
17. Diker-Cohen, T., Rosenberg, D., Avni, T., et al. (2020). Risk for infections during treatment with denosumab for osteoporosis: A systematic review and meta-analysis. *Journal of Clinical Endocrinology & Metabolism, 105*(5), 1641–1658. https://doi.org/10.1210/clinem/dgz322
18. Eastell, R., Christiansen, C., Grauer, A., et al. (2011). Effects of denosumab on bone turnover markers in postmenopausal osteoporosis. *Journal of Bone and Mineral Research, 26*(3), 530–537. https://doi.org/10.1002/jbmr.251

19. Eastell, R., O'Neill, T. W., Hofbauer, L. C., et al. (2016). Postmenopausal osteoporosis. *Nature Reviews Disease Primers, 2*, 16069. https://doi.org/10.1038/nrdp.2016.69
20. Ferrari, S., Adachi, J. D., Lippuner, K., et al. (2015). Further reductions in nonvertebral fracture rate with long-term denosumab treatment in the FREEDOM open-label extension and influence of hip bone mineral density after 3 years. *Osteoporosis International, 26*, 2763–2771. https://doi.org/10.1007/s00198-015-3179-x
21. Fizazi, K., Carducci, M., Smith, M., et al. (2011). Denosumab versus zoledronic acid for treatment of bone metastases in men with castration-resistant prostate cancer: A randomised, double-blind study. *The Lancet, 377*(9768), 813–822. https://doi.org/10.1016/S0140-6736(10)62344-6
22. Hanley, D. A., Adachi, J. D., Bell, A., & Brown, V. (2012). Denosumab: Mechanism of action and clinical outcomes. *International Journal of Clinical Practice, 66*(12), 1139–1146. https://doi.org/10.1111/ijcp.12022
23. Hasenfratz, M., Mellert, K., Marienfeld, R., et al. (2021). Profiling of three H3F3A-mutated and denosumab-treated giant cell tumors of bone points to diverging pathways during progression and malignant transformation. *Scientific Reports, 11*, 5709. https://doi.org/10.1038/s41598-021-85319-x
24. Kanis, J. A., Norton, N., Harvey, N. C., et al. (2021). SCOPE 2021: A new scorecard for osteoporosis in Europe. *Archives of Osteoporosis, 16*, 82. https://doi.org/10.1007/s11657-020-00871-9
25. Kazandjian, D. (2016). Multiple myeloma epidemiology and survival: A unique malignancy. *Seminars in Oncology, 43*(6), 676–681. https://doi.org/10.1053/j.seminoncol.2016.11.004
26. Kendler, D. L., Cosman, F., Stad, R. K., & Ferrari, S. (2022). Denosumab in the treatment of osteoporosis: 10 years later: A narrative review. *Advances in Therapy, 39*, 58–74. https://doi.org/10.1007/s12325-021-01936-y
27. Khan, A. A., Morrison, A., Hanley, D. A., et al. (2015). Diagnosis and management of osteonecrosis of the jaw: A systematic review and international consensus. *Journal of Bone and Mineral Research, 30*(1), 3–23. https://doi.org/10.1002/jbmr.2405
28. Li, H., Gao, J., Gao, Y., et al. (2020). Denosumab in giant cell tumor of bone: Current status and pitfalls. *Frontiers in Oncology, 10*, 580605. https://doi.org/10.3389/fonc.2020.580605
29. López-Pousa, A., Martín Broto, J., Garrido, T., & Vázquez, J. (2015). Giant cell tumour of bone: New treatments in development. *Clinical and Translational Oncology, 17*, 419–430. https://doi.org/10.1007/s12094-014-1268-5
30. McDonald, M. M., Khoo, W. H., Ng, P. Y., et al. (2021). Osteoclasts recycle via osteomorphs during RANKL-stimulated bone resorption. *Cell, 184*(5), 1330–1347.e13. https://doi.org/10.1016/j.cell.2021.02.002
31. Parmeggiani, A., Miceli, M., Errani, C., & Facchini, G. (2021). State of the art and new concepts in giant cell tumor of bone: Imaging features and tumor characteristics. *Cancers, 13*(24), 6298. https://doi.org/10.3390/cancers13246298
32. Raje, N., Terpos, E., Willenbacher, W., et al. (2018). Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: An international, double-blind, double-dummy, randomised, controlled, phase 3 study. *The Lancet Oncology, 19*(3), 370–381. https://doi.org/10.1016/S1470-2045(18)30072-X
33. Rajkumar, S. V. (2020). Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *American Journal of Hematology, 95*(5), 548–567. https://doi.org/10.1002/ajh.25791
34. Roodman, G. D. (2010). Pathogenesis of myeloma bone disease. *Journal of Cellular Biochemistry, 109*(2), 283–291. https://doi.org/10.1002/jcb.22403
35. Ruggiero, S. L., Dodson, T. B., Aghaloo, T., et al. (2022). American Association of Oral and Maxillofacial Surgeons' position paper on medication-related osteonecrosis of the jaws—2022 update. *Journal of Oral and Maxillofacial Surgery, 80*(5), 920–943. https://doi.org/10.1016/j.joms.2022.02.008
36. Russell, R. G. G. (2007). Bisphosphonates: Mode of action and pharmacology. *Pediatrics, 119*(Suppl. 2), S150–S162. https://doi.org/10.1542/peds.2006-2023H
37. Saad, F., Brown, J. E., Van Poznak, C., et al. (2012). Incidence, risk factors, and outcomes of osteonecrosis of the jaw: Integrated analysis from three blinded active-controlled phase III trials in cancer patients with bone metastases. *Annals of Oncology, 23*(5), 1341–1347. https://doi.org/10.1093/annonc/mdr435
38. Shane, E., Burr, D., Abrahamsen, B., et al. (2014). Atypical subtrochanteric and diaphyseal femoral fractures: Second report of a task force of the American Society for Bone and Mineral Research. *Journal of Bone and Mineral Research, 29*(1), 1–23. https://doi.org/10.1002/jbmr.1998
39. Sozen, T., Ozisik, L., & Basaran, N. C. (2017). An overview and management of osteoporosis. *European Journal of Rheumatology, 4*(1), 46–56. https://doi.org/10.5152/eurjrheum.2016.048
40. Stopeck, A. T., Lipton, A., Body, J. J., et al. (2010). Denosumab compared with zoledronic acid for the treatment of bone metastases in patients with advanced breast cancer: A randomized, double-blind study. *Journal of Clinical Oncology, 28*(35), 5132–5139. https://doi.org/10.1200/JCO.2010.29.7101
41. Terpos, E., Morgan, G., Dimopoulos, M. A., et al. (2021). Treatment of multiple myeloma-related bone disease: Recommendations from the International Myeloma Working Group. *The Lancet Oncology, 22*(3), e119–e130. https://doi.org/10.1016/S1470-2045(20)30559-3
42. Tsourdi, E., Zillikens, M. C., Meier, C., et al. (2021). Fracture risk and management of discontinuation of denosumab therapy: A systematic review and position statement by ECTS. *Journal of Clinical Endocrinology & Metabolism, 106*(1), 264–281. https://doi.org/10.1210/clinem/dgaa756
43. Weilbaecher, K. N., Guise, T. A., & McCauley, L. K. (2011). Cancer to bone: A fatal attraction. *Nature Reviews Cancer, 11*, 411–425. https://doi.org/10.1038/nrc3055
44. Yamamoto, H., Ishihara, S., Toda, Y., & Oda, Y. (2020). Histone H3.3 mutation in giant cell tumor of bone: An update in pathology. *Medical Molecular Morphology, 53*, 1–6. https://doi.org/10.1007/s00795-019-00238-1