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Review Article

Osteonecrosis of the Jaw Associated with Long-Term Denosumab Therapy: A Review of Published Cases

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Abstract

Background: Denosumab, a monoclonal antibody against RANKL, is used at high dose for skeletal-related events in oncology and at low dose for osteoporosis, but both regimens carry a risk of medication-related osteonecrosis of the jaw (MRONJ).

Objective: To review published case reports/series and the epidemiologic, mechanistic and guideline literature on denosumab-associated MRONJ, contrasting oncologic and osteoporosis populations.

Methods: Narrative review of case reports, case series, randomized trials, retrospective cohorts, and guidelines.

Findings: Pooled oncology-trial data show MRONJ in 1.8% of denosumab-treated versus 1.3% of zoledronic acid-treated patients; a 20-year breast cancer cohort found 12% incidence with denosumab versus 3% with bisphosphonates. Published cases span multi-year high-dose oncologic exposure to osteoporosis patients developing MRONJ after a single low dose, often extraction-triggered. Unlike bisphosphonates, denosumab's effect is reversible, informing but not resolving the drug-holiday debate.

Conclusions: Pre-therapy dental screening, AAOMS-staged diagnosis, and conservative-first management with surgery reserved for refractory disease remain the evidence base; drug holidays lack proven benefit.

Keywords: Denosumab; Osteonecrosis of the jaw; RANKL; Bone-modifying agents; MRONJ

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Introduction

Denosumab inhibits receptor activator of nuclear factor-κB ligand (RANKL), blocking osteoclast differentiation and activity. It is approved at high dose (120 mg monthly, as Xgeva) for skeletal-related events in bone metastases, giant cell tumour of bone and hypercalcemia of malignancy, and at low dose (60 mg every 6 months, as Prolia) for osteoporosis. Both regimens are associated with medication-related osteonecrosis of the jaw (MRONJ), a complication first linked to bisphosphonates and subsequently, as antiresorptive pharmacology diversified, renamed by the American Association of Oral and Maxillofacial Surgeons (AAOMS) to reflect denosumab and antiangiogenic agents as additional causes [1].

This narrative review surveys the published literature — individual case reports and case series, randomized trials, retrospective cohorts, and guideline documents — on denosumab-associated MRONJ, with attention to both oncologic and osteoporosis populations and to the pathophysiologic and management questions specific to a reversible RANKL inhibitor rather than a bone-bound bisphosphonate. As with bisphosphonate-associated osteonecrosis, the individual case-report literature remains an important source of clinical detail — triggering events, staging, and treatment response — that large registries and pooled trial analyses cannot capture at the patient level, and it is this literature the present review foregrounds.

Epidemiology

The pivotal head-to-head oncology trials established the incidence baseline. A combined analysis of three blinded phase III trials (5,723 patients with bone metastases from solid tumours or myeloma) found MRONJ in 1.8% of denosumab-treated and 1.3% of zoledronic acid-treated patients (P=0.13), with extraction preceding 61.8% of cases and resolution in 36.0% overall [2]. These trials — denosumab versus zoledronic acid in advanced breast cancer [3] and in castration-resistant prostate cancer [4] — defined the high-dose oncologic exposure population from which most oncologic MRONJ cases, including Tomic's severe stage 3 case [5], subsequently arise.

In the osteoporosis setting, incidence is lower but still measurable, and long-term real-world data increasingly suggest denosumab is not necessarily safer than bisphosphonates. A 20-year population-based Austrian cohort of breast-cancer patients with bone metastases found MRONJ in 12% of those on denosumab versus 3%

on bisphosphonates alone, rising to 16% with sequential bisphosphonate-then-denosumab exposure [6]. Conversely, a Taiwanese multi-institutional cohort of osteoporotic patients found a lower long-term risk with denosumab than bisphosphonates (1.47 vs 2.49 per 1,000 person-years) [7], and a Spanish longitudinal series similarly documented denosumab-associated MRONJ in osteoporosis, though at markedly lower absolute rates than in oncologic dosing [8]. A French retrospective single-centre study of denosumab-only regimens further characterised the occurrence rate and timing of denosumab-related MRONJ [9]. These discordant risk comparisons likely reflect differences in dose, dosing interval, cumulative bisphosphonate pre-exposure and ascertainment, all of which recur as themes in the individual case literature below. Notably, several of the discordant findings involve patients who received bisphosphonates before switching to denosumab — a sequencing pattern common in both oncology (where denosumab superseded zoledronic acid as preferred first-line therapy after the head-to-head trials) and osteoporosis (where denosumab is often introduced after years of oral bisphosphonate). Because bisphosphonate exposure persists in bone for years after discontinuation, patients transitioning to denosumab effectively receive combined antiresorptive suppression, which may explain both the higher combined-exposure risk in the Brunner cohort and the unusually short denosumab exposure preceding several of the individual cases reviewed below.

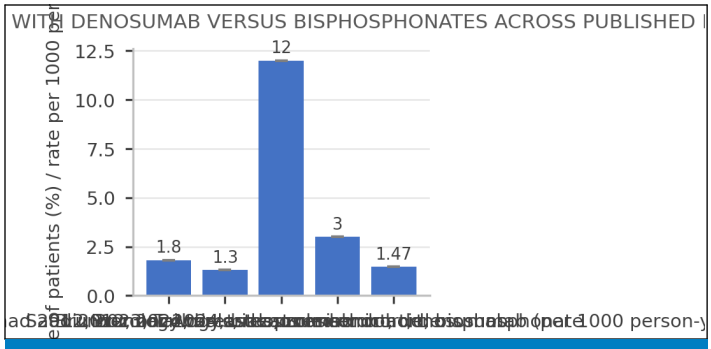

Figure 1: Reported MRONJ incidence with denosumab versus bisphosphonates: 1.8% vs 1.3% in pooled oncology trials [2]; 12% vs 3% in a 20-year breast cancer cohort [6]; 1.47 per 1000 person-years with denosumab in a Taiwanese osteoporosis cohort [7].

Pathophysiology

Denosumab binds RANKL with high affinity, preventing RANK activation on osteoclast precursors and mature osteoclasts, thereby suppressing osteoclast formation, function and survival [10]. This differs mechanistically from bisphosphonates, which bind hydroxyapatite and are internalised by osteoclasts, persisting in bone matrix for years. Denosumab is not bone-bound; its antiresorptive effect is pharmacologically reversible within months of the last dose, and discontinuation after long-term use produces a turnover "rebound" with risk of multiple vertebral fractures [11]. This reversibility is central to clinical decisions about denosumab timing around dental procedures and to the biological plausibility, if not proven benefit, of a drug holiday.

The leading pathogenic model for MRONJ more broadly implicates over-suppressed bone remodelling unable to repair microdamage from mastication, compounded by an infection/acidic-microenvironment mechanism in which local infection and low pH potentiate cellular toxicity to osteoclasts, osteoblasts, fibroblasts and angiogenic cells [12]. Because denosumab lacks bisphosphonates' bone affinity and pH-dependent release, its pathogenic contribution is thought to act principally through profound RANKL blockade rather than through a local chemical reservoir effect — a distinction invoked to explain why some

denosumab-associated cases (e.g., Qaisi's rapidly progressive soft-palate necrosis after a single dose [13], and Papadimitriou's and Száraz's single-dose cases [14,15]) can develop unusually quickly, particularly after prior bisphosphonate priming.

Clinical Presentation

Published cases span the oncologic and osteoporosis spectrum described in the accompanying case table. At the severe end, Tomic reported stage 3 MRONJ of the entire lower jaw in a 71-year-old man on monthly high-dose denosumab for metastatic melanoma, with pain, paresthesia and poor general condition [5], while Qaisi described a 65-year-old woman who developed a life-threatening MRONJ with spontaneous soft-palate necrosis and sepsis shortly after switching from bisphosphonate to a single dose of denosumab around an extraction [13]. At the milder end, Bettini described stage 2 maxillary MRONJ in a patient with cancer treatment-induced bone loss, successfully managed with a minimally invasive approach after temporary denosumab suspension [16], and Goss described a similarly limited stage 2 presentation managed with sequestrectomy guided by C-terminal telopeptide (CTX) normalisation [17].

Table 1: Published cases and case series of denosumab-associated medication-related osteonecrosis of the jaw reviewed here [5,14,15,20,13,28,18,19,16,17]; N = 10 reports.

Report	Age/sex	Indication	Denosumab exposure	Trigger	Stage	Outcome
Tomic 2019	71/M	Oncologic (melanoma)	Long-term, monthly high-dose	Not stated	3	Near-complete regression
Papadimitriou 2024	75/F	Osteoporosis	Single dose	Not stated	Not stated	Not stated
Száraz 2024	Not stated	Osteoporosis	Single dose	Not stated	Not stated	MRONJ at ~3 months
de Sales Lima 2018	Postmenopausal/F	Osteoporosis	Not stated	Dental implant	Not stated	No complications at 8 months
Qaisi 2016	65/F	Osteoporosis	Single dose	Extraction	Not stated (life-threatening)	Near-complete recovery at 1 yr
Rachner 2013	Not stated	Osteoporosis	Not stated	Not stated	Not stated	Not stated
Falinda 2022, n=6	Not stated	Mixed cancer/osteoporosis	Not stated	Extraction (4 of 6)	4 stage 2, 2 stage 3	Not stated
Jung 2022, n=4	Not stated	Osteoporosis	Variable	Extraction	Not stated	Not stated
Bettini 2022	Not stated	Secondary osteoporosis (CTIBL)	Suspended 7 months prior	Not stated	2	Favourable healing
Goss 2022	Not stated	Not stated	Not stated	Not stated	2	Healed

A recurring theme is MRONJ developing after strikingly short denosumab exposure — a single dose in Papadimitriou's, Száraz's and effectively Qaisi's cases, each following years of prior oral bisphosphonate — suggesting bisphosphonate pre-treatment may lower the threshold for denosumab-triggered disease [14,15,13]. The Edinburgh series of seven patients, all bisphosphonate-pre-exposed, found six developed MRONJ (four stage 2, two stage 3), most within 8-20 weeks of dental extraction [18], and a Korean cohort study similarly tabulated individual extraction-triggered cases, including one diagnosed six months after the last dose [19]. de Sales Lima's case, centred on a dental implant site rather than extraction, illustrates that peri-implant tissue is also a recognised trigger [20].

Diagnostic Approach and Staging

Diagnosis is clinical: exposed bone, or bone probeable through a fistula in the maxillofacial region, persisting more than 8 weeks in a patient exposed to an antiresorptive or antiangiogenic agent without a history of jaw irradiation [1]. The AAOMS 2022 update retains a four-tier staging system — Stage 0 (non-specific

symptoms/findings without exposed bone), Stage 1 (exposed bone, asymptomatic), Stage 2 (exposed bone with pain and infection), and Stage 3 (exposed bone with pain, infection, and pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border) — used consistently across the case literature (e.g., Tomic's stage 3, Bettini's and Goss's stage 2, Falinda's stage 2/3 series) [1,5,16,17,18]. An earlier international consensus statement established analogous diagnostic criteria and staging guidance across bisphosphonate- and denosumab-associated disease [21]. A 2025 MASCC/ISOO clinical practice statement addresses the specific role of imaging and laboratory testing, including CTX, in diagnosis, staging and monitoring, while cautioning that CTX has not been validated as a reliable predictor of individual risk [22].

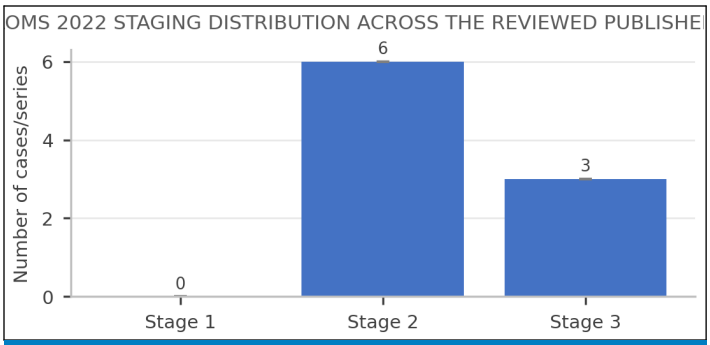

Figure 2: AAOMS 2022 stage distribution among the published cases and case series reviewed here (Table 1): stage 2 in 6 cases, stage 3 in 3 cases [1,5,16,17,18].

Management, Including Refractory Cases

First-line prevention is a pre-therapy dental assessment and completion of any necessary extractions or restorative work before starting denosumab, per MASCC/ISOO/ASCO guidance for oncologic bone-modifying agents [23]; general dental and osteoporosis guidance extends the same risk-reduction principle to low-dose regimens, recommending optimisation of oral hygiene and elimination of active dental disease before the first injection wherever feasible, since screening after therapy has begun cannot undo cumulative exposure. Once MRONJ is established, management is predominantly conservative — analgesia, antimicrobial rinses/therapy, and observation — with surgery (debridement, sequestrectomy or resection) reserved for refractory, stage 2-3, or progressive disease, as illustrated by Goss's sequestrectomy [17], de Sales Lima's implant-site resection [20], and Bettini's minimally invasive extraction after suspension [16].

Table 2: Key evidence on drug holidays and management strategy in denosumab-associated MRONJ [24,25,1,26].

Source	Design	Key finding	Implication
Aboalela 2022	Systematic review/meta-analysis	Drug holidays did not consistently reduce MRONJ risk after extraction	No proven benefit to holidays
Sawada 2023	Immunohistochemical study, n=7	Incomplete osteoclast recovery despite prolonged holiday	Holiday duration may be biologically insufficient
AAOMS 2022	Position paper	No committee consensus reached on drug holidays	Guideline-level uncertainty persists
Hoefert 2017	Retrospective cohort	Major surgery gave more complete healing than non-operative care; cessation did not improve healing	Surgery, not cessation, drives resolution

The drug-holiday question remains unresolved and is specific to denosumab's reversibility. Because denosumab does not persist in bone, a temporary suspension timed to the next scheduled dose is biologically plausible for elective procedures, and Bettini's and Tomic's cases used prolonged denosumab suspension as part of MRONJ management with apparent benefit [16,5]. However, a systematic review and meta-analysis of drug holidays across antiresorptive agents found no consistent reduction in MRONJ risk after extraction, whether for bisphosphonates or denosumab [24], and an

immunohistochemical study of seven high-dose denosumab patients undergoing segmental mandibulectomy found incomplete osteoclast recovery even after prolonged holidays, questioning whether a holiday of any feasible duration reliably restores bone turnover before extraction [25]. The AAOMS 2022 update likewise could not reach committee consensus on drug holidays [1]. Discontinuation is not without its own risk: stopping long-term denosumab produces a turnover rebound and elevated vertebral fracture risk, documented in the pivotal discontinuation-observation study [11] and echoed clinically in Tomic's patient, who suffered a vertebral fracture during a prolonged antiresorptive break [5].

Outcomes and Prognosis

Outcomes reported across these cases range from near-complete regression with conservative therapy alone [5,13] to uneventful healing after limited surgery [20,16,17]. A retrospective cohort of operatively versus non-operatively managed denosumab-related osteonecrosis found major surgery associated with more complete healing than conservative management, while denosumab cessation itself did not improve healing outcomes — reinforcing that surgical debridement, not drug interruption, drives resolution in established disease [26]. This surgical-benefit signal is echoed in the Edinburgh series, where staged disease (stage 2/3) predominated among bisphosphonate-pre-exposed patients and most lesions followed extraction rather than arising spontaneously, again pointing to local surgical trauma as the proximate trigger superimposed on suppressed remodelling [18]. The pivotal FREEDOM trial establishing long-term low-dose denosumab in postmenopausal osteoporosis reported very low absolute MRONJ numbers over its multi-year duration, underscoring that while risk is real and appears in individual published cases, most osteoporosis patients tolerate long-term therapy without this complication [27].

Conclusion

The published case literature confirms that denosumab-associated MRONJ occurs across the full dose spectrum, from monthly high-dose oncologic regimens to a single low-dose osteoporosis injection, particularly after bisphosphonate pre-exposure. Incidence estimates vary widely by population and study design, from under 2% in pooled oncology trials to double-digit percentages in some real-world cohorts. Denosumab's pharmacologic reversibility distinguishes its biology from bisphosphonates but has not translated into a proven drug-holiday benefit. Management remains staged and predominantly conservative, with surgery reserved for refractory or advanced disease, and prevention through pre-therapy dental optimisation remains the most consistently endorsed strategy across guidelines.

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