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Bisphosphonate Osteonecrosis in Clinical Practice: A Scoping Review with Special Emphasis on Pamidronate Therapy

*Alper Sevinc**

Clinic of Medical Oncology, Gaziantep Medicalpoint Hospital, Gaziantep, Turkiye

Abstract

Osteonecrosis of the Jaws (ONJ) is a rare but important complication of exposure to bisphosphonates, specifically in the oncology setting with high-dose/long-term usage. Bisphosphonate-induced ONJ, referred to as Bisphosphonate Osteonecrosis (BON), leads to adverse health outcomes such as pain, discomfort and poor quality of life and compromises the optimal benefit of the treatment. The exact pathophysiology of ONJ remains unclarified, in addition to absence of well-established risk factors and predictors of disease prognosis and outcomes. This scoping review aimed to address the properties and therapeutic indications of pamidronate amongst the other bisphosphates, and the clinical manifestations, pathogenesis and risk factors and management of BON, and to summarize the current evidence on the prevalence of ONJ in clinical practice as a function of treatment indication, and type and duration of antiresorptive agent as well as the bisphosphonate therapy after development of ONJ. Pamidronate seems to be associated with a much lower risk and a later onset of ONJ than zoledronate, possibly due to its less potent inhibitory effect on bone turnover and a weaker anti-resorptive activity. Nonetheless, the dose and duration of bisphosphonate is considered a major risk factor for the BON development, with more potent agents increasing the risk with shorter durations of exposure.

Keywords: Bisphosphonates; Pamidronate; Osteonecrosis of the jaws; Bisphosphonate osteonecrosis; Clinical manifestation; Management

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Correspondence:
Dr. Alper Sevinc, Clinic of Medical Oncology, Gaziantep Medicalpoint Hospital Mücahitler, 52063. Sk. No: 2, 27584 Şehitkamil, Gaziantep, Turkiye, Tel: +90 555 241 46 87;

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Introduction

Bisphosphonates are antiresorptive agents that act by inhibiting bone reabsorption via suppression of osteoclast activity, in addition to their antiangiogenic effect [1-3]. Hence, they are widely used in clinical practice for the management of diseases involving bone reabsorption (i.e., osteoporosis or Paget's disease; usually via the oral route), or bone metastases and malignancy-related hypercalcemia (i.e., multiple myeloma and bone metastases secondary to solid tumors; via the intravenous route) [1,3,4]. While bisphosphonates have been used in clinical practice for more than three decades, recently, there has been growing interest in their association with the risk of Osteonecrosis of the Jaws (ONJ) which appears as a long-term complication of bisphosphonate exposure [2,5,6]. Currently, bisphosphonates are considered the most common cause of medication-related ONJ (MRONJ), which occurs due to their effects on bone remodeling, angiogenesis, infection, inflammation and soft tissue toxicity [6,7]. ONJ induced specifically by bisphosphonates, namely the bisphosphonate osteonecrosis (BON), refers to a condition characterized by exposure of bone in mandible or maxilla persisting for more than 8 weeks in patients who have received treatment with bisphosphonates in the absence of maxillary radiotherapy [1,2,5,6,8]. The exact pathogenesis of MRONJ remains unknown, in addition to the current paucity of information on the true incidence, risk factors, disease prognosis and outcomes and preventive and therapeutic approaches of BON [5,7,9-12]. This scoping review aimed to address the properties and therapeutic indications of pamidronate amongst the other bisphosphates, and the clinical manifestations, pathogenesis and risk factors and management of BON, and to summarize the current evidence on the prevalence of ONJ in clinical practice as a function of treatment indication, and type and duration of antiresorptive agent as well as the bisphosphonate therapy after development of ONJ.

Properties and Therapeutic Indications of Pamidronate Amongst Other Bisphosphonates

Chemical structure and mechanism of action

Bisphosphonates are chemically stable derivatives of inorganic pyrophosphate with ability to bind to bone and inhibit osteoclast function [10,13,14]. Owing to their ability to bind divalent ions such as Ca2+, they dock in hydroxyapatite-binding sites on active bone mineral surfaces undergoing osteoclastic bone resorption [12,15-17]. Hence, they liberate during osteoclasts-mediated resorption of bisphosphonate-impregnated bone, resulting in their effective uptake by osteoclasts via endocytosis, which ultimately leads to apoptosis inhibiting the osteoclast function [10,13-15,18]. The structure of bisphosphonates comprises the basic P-C-P core with two side chains (R1, R2) bound to the carbon atom [10,13,14,17,19]. Depending on the presence or absence of a nitrogen atom located in the R2 group, they are classified as non-nitrogen-containing and nitrogen-containing bisphosphonates. Non-nitrogen-containing bisphosphonates include the first-generation etidronate, clodronate, and tiludronate, while nitrogen-containing bisphosphonates include second-generation (pamidronate, alendronate, ibandronate) and third-generation (risedronate and zoledronate) bisphosphonates, differing in the mechanism of action on osteoclasts and antiresorptive activities (Table 1) [3,10,16,17-20]. Non-nitrogen-containing bisphosphonates are metabolized to nonhydrolyzable ATP analogues, which are cytotoxic to osteoclasts because they inhibit multiple ATP-dependent cellular processes, leading to osteoclast apoptosis [3,16,18,20]. However, pamidronate as other nitrogen-containing bisphosphonates inhibit the activity of farnesyl pyrophosphate synthase inside the osteoclasts and thereby the posttranslational modification of proteins with central roles in the regulation of core osteoclast cellular activities, which ultimately leads to osteoclast apoptosis [10,15,16,18,20,21]. In addition, they also reduce recruitment of osteoclasts and induce osteoblasts to produce an osteoclast-inhibiting factor (Table 1) [6,22,23].

Therapeutic indications

Targeting the osteoclast with antiresorptive agents is currently the mainstay treatment for a spectrum of bone diseases with an imbalance of bone turnover ranging from the osteoporosis (fragility fractures) and other benign bone diseases (i.e., Paget's disease of bone and osteogenesis imperfecta) to the bone disorders in the oncology setting such as cancer treatment-induced bone loss (CTIBL), hypercalcemia of malignancy and skeletal-related events (SREs; pathologic fracture, radiation to bone, surgery to bone, and spinal cord compression) in the context of advanced solid tumors (i.e., breast, prostate, and lung cancers) and multiple myeloma [5,10-12]. In general, oral bisphosphonates (alendronate, risedronate, clodronate and ibandronate) are preferred in osteoporosis and other benign bone diseases, whereas IV bisphosphonates (ibandronate, pamidronate and zoledronate) are mostly used for prevention of CTIBL and the management of bone metastasis. Ibandronate and zoledronic acid have also been approved for IV administration to treat postmenopausal osteoporosis (Table 1) [1,5,8,10,11,16,24]. Pamidronate is the first of the second-generation amino bisphosphonates approved by FDA in 1996 [25]. FDA-approved indications for pamidronate include hypercalcemia of malignancy, Paget disease of bone, osteolytic bone metastases of breast cancer, and osteolytic lesions of multiple myeloma [26]. Non-FDA-approved indications include osteoporosis, bone loss, complex regional pain syndrome, nonmetastatic hormone-responsive prostate cancer, and osteogenesis imperfecta in children [26]. The treatment schedule for specific indications include use of IV pamidronate as 90 mg infusions for at least 2 hours (repeated every 3 to 4 weeks) for osteolytic lesions of multiple myeloma and bone metastases of breast cancer [27,28], a single dose of 90 mg IV pamidronate for 2 to 24 hours for hypercalcemia of malignancy [29] and use of IV pamidronate as 30 mg over 4 hours (on three consecutive days) or 60 to 90 mg infusion over 2 to 4 hours (for two or more nonconsecutive days) for the Paget disease of bone [30]. Although nitrogen-containing bisphosphonates are considered to be more potent than the non–nitrogen-containing bisphosphonates, their ability to suppress osteoclast activity varies and the relevance of superior suppression of bone turnover in terms of better fracture prevention remains to be determined [10]. Indeed, adherence to long-term bisphosphonate therapy, rather than the specific bisphosphonate used, is considered the most important factor in determining the effectiveness of treatment for limiting fracture risk [10,31,32].

Clinical manifestations of bisphosphonate osteonecrosis

Proper medical history and clinical examination remain the most sensitive diagnostic tools for BON, and the presenting signs and symptoms may include local pain, bone and/or gingival swelling, erythema, tooth mobility, tooth abscess, ulceration, altered sensation and even paresthesia or anesthesia of the associated branch of the trigeminal nerve [5,6,11,33,34-36]. However, exposed bone may remain asymptomatic for a for prolonged periods of or clinical signs and symptoms may manifest before clinically detectable ONJ develops [2,5,11,36,37]. Given that early signs of BON (sinus pain, odontalgia, and altered neurosensory function) are nonspecific and a high index of suspicion is required, the diagnostic delay is common [5,8,11,36]. Later findings are suggested to include fistulae development or chronic maxillary sinusitis along with deterioration in oral and general Quality of Life (QoL) due to pain, chewing and speech difficulties, weight loss, and socializing issues, which worsens with advancing of ONJ stage [11,38-40].The radiographic findings (areas of focal sclerosis, thickened lamina dura and reactive periosteal bone) are non-specific and variable, and in the absence of bone exposure, these findings alone are not considered as sufficient to diagnose BON [2,33,34,41]. As per diagnostic criteria defined in 2014 by AAOMS, the persistence of exposed bone in the oral cavity for 8 weeks or longer without any response to appropriate therapy is the hallmark of MRONJ [5,6,42]. The current staging system within this definition of MRONJ (AAOMS, 2014) comprises four stages (stages 0-3) of increasing severity, ranging from stage 0 (no clinical evidence of necrotic bone) up to stage 3 (severe complications such as fractures, extra oral fistulae, necrosis beyond the alveolar region) [5,8]. Presence of manifestations, even in the absence of bone exposure (equivalent to stage 0) is considered indicative of prodromal BON, while up to 50% of these patients may progress towards disease stages 1 to 3 over time [5,8].

Pathogenesis and Risk Factors for Bisphosphonate Osteonecrosis

Predisposition for ONJ in the alveolar bone of jaws

Bone turnover suppression is the main mechanism used by antiresorptive agents to increase bone density and reduce fracture risk, while the osteoclast differentiation and functionality, and a degree of bone remodeling, is of critical importance for bone

Table 1: Classification and Mechanism of bisphosphonates and indications [6,10,11,17,19].

Structure	Generic name	Class	Mechanism of osteoclasts apoptosis	Route
Non-nitrogen bisphosphonates	Etidronate	First generation	↑ nonhydrolyzable ATP analogues	Oral
	Clodronate			Oral
	Tiludronate			Oral
Nitrogen-bisphosphonates	Pamidronate	Second generation	inhibition of FPPS	IV
	Alendronate			Oral
	Ibandronate			Oral, IV
	Risedronate	Third generation	inhibition of FPPS	Oral
	Zoledronate		↑ production of OIF	IV

FPPS: Farnesyl Pyrophosphate Synthase; OIF: Osteoclast-Inhibiting Factor

healing and repair [11]. The osteonecrosis occurs primarily within the alveolar bone of the jaws but not in other skeletal sites, and this predisposition is considered to be related to the greater uptake of bisphosphonates and higher remodeling rate in alveolar bone of the jaws than in other bones, as well as to the repetitive chewing-based microtraumas [6,11,43,44]. If more bisphosphonate accumulates in the presence of a continued demand of remodeling or trauma (i.e., tooth extraction), the alveolar bone, which eventually fails to respond with new bone from osteoclastic bone resorption followed by new bone formation, becomes necrotic. Afterwards, the overlying bone is deprived of its blood supply from underlying bone and breaks down, resulting in clinically exposed bone [6].

Pathogenesis

The pathogenesis of MRONJ is considered multifactorial with participation of several potential mechanisms such as over-suppression of bone remodeling, local inflammation and infections, angiogenesis inhibition, innate or acquired immune dysfunction, soft-tissue toxicity and genetic predisposition, infection, immune dysfunction, inflammation, vascular effect, drug interactions, and genetic predisposition [1,5,11,42,45-47]. Although an interplay between an antiresorptive medication and inflammation or infection is considered necessary and sufficient to induce MRONJ, accumulating evidence indicates that MRONJ is a multifactorial disease with contribution of several potential mechanisms in the overall pathophysiology [5,42,46].

Risk factors and prognostic indicators

Currently, there are no well-established predictors for increased risk of BON in individuals taking bisphosphonates or prognostic indicators predictive of outcomes, other than the greater risk attributed to the use of intravenous bisphosphonates for cancer rather than the use of oral bisphosphonates for osteoporosis or Paget's disease, and a correlation between dosage/duration of therapy and the occurrence of BON [6,11,48]. Even in cancer patients, BON incidence differs with respect to bisphosphonate doses with higher risk considered for the higher cumulative doses used for treatment of bone metastasis than the doses used for CTIBL prevention [11]. Overall, treatment regimen (high-dose therapy), treatment duration (≥3 years) in those treated with low-dose regimen, prior use of bisphosphonates, use of corticosteroids, chemotherapy or angiogenesis inhibitors, radiotherapy to head and neck, presence of poor oral hygiene, periodontitis or ill-fitting dentures, smoking, comorbidities (i.e., cancer, anemia, diabetes mellitus, immunological disorders and renal failure) are suggested to be associated with elevated MRONJ risk [12]. Patients who have received low-dose therapy for less than 3 years or are scheduled to receive low-dose therapy and have no additional risk factors are regarded as being at low risk of development of MRONJ [12]. In general, the risk factors for MRONJ are suggested to be classified as local factors (bone-invasive dental treatment such as tooth extraction or dental implants, dental infection, periodontal disease, ill-fitting dentures or prostheses), drug factors (potency of bisphosphonate/ other antiresorptive agents, route of application, dose, frequency and cumulative exposure, use of corticosteroids, anti-angiogenic drugs, chemotherapy), systemic factors (primary disease [solid tumors, multiple myeloma, osteoporosis], comorbid diseases [diabetes, rheumatoid arthritis, obesity, anemia, previous atypical femoral fracture, hyperparathyroidism, renal dialysis, HIV infection, Sjogren's syndrome] and smoking) and genetic factors (Table 2) [3,11,12,33,34,49]. The ONJ-risk factors in the oncology population, in decreasing order of importance, are suggested to include use of IV bisphosphonates (cumulative dose and duration of exposure), use of denosumab (cumulative dose and duration of exposure), radiation therapy, dental extraction, chemotherapy, periodontal disease, use of oral bisphosphonates, osteoporosis, local suppuration, glucocorticoid therapy, diabetes, denture use, erythropoietin therapy, smoking, hyperthyroidism, renal dialysis, cyclophosphamide therapy and increasing age [33,34]. In the osteoporosis patient population, a smaller number of risk factors for the development of ONJ are considered which include, in decreasing order of importance, suppuration, use of bisphosphonates (duration of treatment), dental extraction and anemia (Table 2) [33,34].

Preventive Measures for Bisphosphonate Osteonecrosis

Given that ONJ is a condition associated with poor oral health, oral surgery, and use of potent antiresorptive agents, optimizing oral health prior to the initiation of bisphosphonates is considered effective in prevention of ONJ [33,34]. Although no individual strategy nor collection of strategies eliminates all MRONJ risks, the preventive procedures related to potentially modifiable factors for reducing the risk of ONJ include performing high-risk surgical procedures prior to commencement of bisphosphonate therapy, using preoperative and postoperative antibiotics and antimicrobial mouth rinses, primarily closing extractions sites and maintaining meticulous oral hygiene, as well as maximizing overall patient health (i.e., smoking cessation and diabetes optimization) [5,6,34,50,51]. Temporary discontinuation of antiresorptive treatment (bisphosphonates or denosumab) in patients requiring invasive dental procedures (referred to as "drug holidays"), although has been accepted and recommended by several international professional societies, is particularly controversial because of low evidence to support strong recommendations [5,11,12, 33,42,49,52-55]. The increased risk of potential deleterious

Table 2: Drug-related, systemic and local risk factors of MRONJ [3,11,12,33,34,49].

Risk Factors of MRONJ		
Drug-related factors	**Systemic factors**	**Local factors**
Potency of bisphosphonates/other antiresorptive agents,	Primary disease (solid tumors, multiple myeloma, osteoporosis)	Bone-invasive dental treatment (tooth extraction or dental implants)
Route of application	Comorbid diseases (diabetes, rheumatoid arthritis, obesity, anemia, previous atypical femoral fracture, hyperparathyroidism, renal dialysis, HIV infection, Sjogren's syndrome)	Dental infection
Dose and frequency	Smoking	Periodontal disease
Cumulative exposure		Ill-fitting dentures or prostheses
Use of corticosteroids, anti-angiogenic drugs, chemotherapy		
Most significant risk factors in the oncology setting in decreasing order of importance		
1. Use of IV bisphosphonates (cumulative dose and duration of exposure)		
2. Use of denosumab (cumulative dose and duration of exposure)		
3. Radiation therapy		
4. Dental extraction		
5. Chemotherapy		
6. Periodontal disease		
7. Use of oral bisphosphonates		
8. Osteoporosis		
9. Local suppuration		
10. Glucocorticoid therapy		
11. Diabetes		
12. Denture use		
13. Erythropoietin therapy		
14. Smoking		
15. Hyperthyroidism		
16. Renal dialysis		
17. Cyclophosphamide therapy		
18. Increasing age		
Most significant risk factors in the osteoporosis setting in decreasing order of importance		
1. Suppuration		
2. Use of bisphosphonates (duration of treatment)		
3. Dental extraction		
4. Anemia		

effects of suspending antiresorptive therapy (i.e., the risk of fracture in osteoporosis patients and the risk of CTIBL and SREs in cancer patients) during drug holidays must be balanced with the reduced risk of development of MRONJ on a case-by-case basis by a multidisciplinary team ensuring the coordination of care between the dentist and the bone specialist or the oncologist [5,11,12,34,49,56].

Management of Bisphosphonate Osteonecrosis

Although, there is no defined treatment algorithm, in general, both in osteoporosis and cancer patients, BON treatment depends on the stage of ONJ and the existing symptoms with consideration of clinical variables likely to influence the outcome (i.e., primary disease, ONJ severity, age, sex, prognosis and life expectancy, comorbidities and estimated bone fragility) to define the optimal therapeutic approach [11,12,53]. The treatment aims to control the infection, progression of bone necrosis and pain, while continuation of treatment in patients receiving high-dose bisphosphonate is considered based on the severity and evolution of ONJ, the oncologic disease burden and activity, and the patient preferences [12,27,42,44,52,57,58].

Conservative medical management

Conservative management approaches include maintenance of optimal oral hygiene via self and regular professional care, treatment of active dental and periodontal diseases, and application of topical antibacterial mouth rinses (chlorhexidine gluconate 0.12%) and systemic antibiotic therapy (penicillin and alternatives such as clindamycin, fluoroquinolones and/or metronidazole), as indicated by local guidelines [1,5,6,8,11,12,33,52,57,59].

Surgical management

In general, the early operative intervention is recommended in patients with failure of nonoperative therapy, while in those with a progressive clinical or radiographic disease or more advanced disease at presentation, surgical resection of ONJ is considered the first-line treatment [5,60,61]. Given the unpredictable progression potential of BON over time, and the likelihood of a nonoperative approach to fail

to uniformly achieve disease resolution, the operative therapy with resection of ONJ lesions has become increasing recognized as a viable option with high success rates and beneficial patient outcomes for all stages of the disease [62-66].

Adjuvant treatment options

In addition to the established conservative and surgical treatment options, several adjuvant treatments for MRONJ have been investigated, including Vitamin E and pentoxifylline, teriparatide hyperbaric oxygen or ozone therapy, laser-assisted surgical debridement/low-level laser therapy and the application of platelet-rich plasma/platelet-derived growth factor (PRP/PRF) to the surgical wound, whereas they are not recommended as a mainstay of treatment until further evidence from prospective controlled clinical trials accumulates to suggest that they can lead to ONJ resolution [5,6,12,33,67-71].

MRONJ in Clinical Practice: Current Evidence by Indication, Type and Duration of Treatment

MRONJ by indication and type of medication

Pamidronate *vs.* other bisphosphonates: In a systematic review of 22 studies on BON in cancer, the mean weighted prevalence of BON was 6.1% (8.6% for zoledronate, 7.3% for pamidronate) overall (n=39,124); 13.3% (9.0% for zoledronate, 10.5% for pamidronate) for studies with documented follow-up (n=927); 0.7% (7.4% for zoledronate, 1.4% for pamidronate) for studies with undocumented follow-up (n=8,829); and 1.2% (10.0% for zoledronate, 4.1% for pamidronate) in epidemiological studies (n=29,368) [72]. The overall prevalence for patients using zoledronic acid only was 8.6%, for pamidronate 7.3%, and 21% for patients who used both (Table 3) [72]. In a case control study (76 cases, 126 controls) to define risk factors associated with ONJ in patients with metastatic cancer treated with bisphosphonates, patients with ONJ were less likely to have received pamidronate than zoledronic acid (OR 0.18, 95% CI: 0.03–0.97, p=0.047) and more likely to have been exposed to bevacizumab (OR 5.15, 95% CI: 1.67–15.95, p=0.005) [45], indicating that ONJ occurs more commonly in the setting of exposure to zoledronic acid than with pamidronate and zoledronic acid or pamidronate alone [45]. In a meta-analysis of 10,694 women who received adjuvant breast cancer therapy with bisphosphonates (n=5,312) or either placebo/no treatment (n=5,382), ONJ was reported only with zoledronate (13 patients, 0.24%) and only in 1 patient in the placebo group (0.02%) but not with clodronate, pamidronate, risedronate or ibandronate, while use of zoledronic acid was significantly associated with increased ONJ risk (OR 3.23, 95% CI=1.7-8) compared with no use (Table 3) [73]. Previous studies in multiple myeloma patients reported low rate of ONJ in patients exposed to pamidronate (0% to 0.05%), a lower rate of ONJ for clodronate (0.5%) than zoledronate (3.7%), as well as similar rates of ONJ for zoledronate (1.3-6.9%) and denosumab (1.1-5.4%) groups (Table 3) [74-80]. Zoledronate has been consistently reported to be a stronger inducer of ONJ when compared with pamidronate [81-87]. While the reason for the association of zoledronic acid with a higher risk of developing ONJ remains unknown, a possible explanation is the more potent inhibitory effect of zoledronic acid on bone turnover and a stronger anti-resorptive activity compared with pamidronate as well as the established antiangiogenic activity [85-88]. However, in a retrospective pharmacovigilance study using the FDA's Adverse Event Reporting System (FAERS) database of 18,421 reports relating to ONJ induced by antiresorptive drugs from January 2004 to September 2021, the reporting Odds ratio (ROR) of ONJ induced by antiresorptive agents (regardless of indication) was higher for pamidronate (ROR=494.8) and zoledronic acid (ROR=431.9), followed by denosumab (ROR=194.8), alendronate (ROR=151.2), risedronate (ROR=140.2), etidronic acid (ROR=64.5), ibandronate (ROR=40.8), and romosozumab (ROR=6.4) [24]. The metabolic bone disorders had the lowest ROR values for each drug, while ROR values were higher for tumor-related indications (mainly for pamidronate and zoledronic acid) and for denosumab than for zoledronic acid, regardless of the indication [24]. Hence, the highest risk of ONJ is related to use of antiresorptive drugs for metastasis, followed by malignancy, while the osteoporosis is associated with the smallest risk [24]. Given that patients with multiple myeloma have the highest incidence of ONJ among all oncology patients receiving bisphosphonate therapy, the choice of bisphosphonate, dosage, and duration of therapy in these patients have been the focus of considerable debate, and the monthly infusion of pamidronate (due to a perceived higher risk of ONJ for zoledronic acid) was favored, with discontinuation after 1 or 2 years of clinical remission [10,89].

Zoledronic acid *vs.* denosumab: In a pooled analysis of three phase 3 clinical trials, comparing denosumab to zoledronic acid in over 5700 patients with breast cancer, prostate cancer, multiple myeloma or solid tumors with bone metastasis, 89 cases of ONJ were documented with similar incidence in the denosumab and zoledronic acid arm (1.8% *vs.* 1.3%) [90]. In patients with advanced breast cancer, the incidence of MRONJ at years 1, 2, and 3, were 0.5%, 1.2%, and 1.4%, respectively in the zoledronic acid group and 0.8%, 1.9%, and 2.0%, respectively in the denosumab group [91]. In patients with metastatic castration-resistant prostate cancer, MRONJ rates in year 1 and year 2 were 1% and 1% for the zoledronic acid and 1% to 2% for the denosumab exposure (Table 3) [92]. In osteoporosis clinical trials, the risk for MRONJ among osteoporotic patients ranges from 0 to 0.02% in the placebo group, and from 0.02 to 0.05% in subjects exposed to bisphosphonates (≤0.02% for IV zoledronate and ≤0.05% for oral bisphosphonates) [93-97]. MRONJ risk among osteoporotic patients exposed to denosumab was reported to be 0.3% (higher than bisphosphonates), after 10 years of follow-up [98], while the risk for MRONJ when exposed to romosozumab (0.03 percent to 0.05 percent) more closely aligns with the risk associated with bisphosphonates [95,96]. The HORIZON Pivotal Fracture trial tested 3,889 randomized patients given annual zoledronic acid versus placebo for 3 years in the setting of postmenopausal osteoporosis; one patient in each group (0.03%) developed MRONJ (Table 3) [99].When zoledronic acid (4 mg, Q4w) was used in metastasis, malignancy, and osteoporosis, the ROR was 79.6, 50.5, and 1.2, respectively [24]. When denosumab (120 mg, Q4w) was used in metastasis, malignancy, and prophylaxis, the ROR was 466.5, 69.4, and 109.7, respectively, while use of denosumab (60 mg, Q6m) in metastasis and osteoporosis was associated with ROR values of 1.3 and 6.5, respectively (Table 3) [24].

MRONJ by duration of therapy

Pamidronate in cancer patients: The duration of antiresorptive therapy is considered a risk factor for developing MRONJ, regardless of indications for therapy [90]. In oncology, the dose and duration of bisphosphonate treatment (particularly >2 years) is considered the most important risk factor for BON development, followed by the type of bisphosphonate [100,101]. In a prospective cohort of 252 cancer patients who received bisphosphonates, 17 patients (6.7%) developed ONJ with no significant difference with respect to primary malignancy (9.9% for multiple myeloma, 2.9% for breast cancer, 6.5%

Table 3: MRONJ prevalence in clinical practice by indication and type of medication.

Indications		Medications				
Solid tumors/multiple myeloma		**Placebo**	**Oral BPs**	**Zoledronate**	**Denosumab**	**Pamidronate**
Peng et al. 2022 [24]			ROR:	ROR:	ROR:	ROR:494.8
			151.2 (alendronate)	431.9 (overall)	194.8 (overall)	
			140.2 (risedronate)	79.6 (metastasis)	466.5 (metastasis)	
			64.5 (etidronic acid)	50.5 malignancy)	69.4 (malignancy)	
			40.8 (ibandronate)			
Saad et al. 2012 [90]				1.30%	1.80%	
Migliorati et al. 2010 [72]	overall			8.60%		7.30%
	documented follow up			9.00%		10.50%
	undocumented follow-up			7.40%		1.40%
	epidemiological studies			10.00%		4.10%
Breast cancer		**Placebo**	**Oral BPs**	**Zoledronate**	**Denosumab**	**Pamidronate**
Stopeck et al. 2010 [91]				0.5% (1 y)	0.8% (1 y)	
				1.2% (2 y)	1.9% (2 y)	
				1.4% (3 y)	2.0% (3 y)	
Mauri et al. 2009 [73]		0.02%	clodronate (0.0%) risedronate (0.0%) ibandronate (0.0%)	0.24%		0.00%
Prostate cancer						
Fizazi et al. 2011 [92]				1% (1 y)	1% (1 y)	
				1% (2 y)	2% (2 y)	
Multiple myeloma		**Placebo**	**Oral BPs**	**Zoledronate**	**Denosumab**	**Pamidronate**
Morgan et al. 2010 [77]			<0.1%	4-3%		
Henry et al. 2011 [78]				1.30%	1.10%	
Raje et al. 2018 [74]				2.80%	4.10%	
Huang et al. 2020 [79]				5.40%	6.90%	
D'Arena et al. 2011 [77]			0.00%			0.00%
Osteoporosis		**Placebo**	**Oral BPs**	**Zoledronate**	**Denosumab**	
Papapoulos et al. 2012 [93]		0.00%			0.04%	
Grbic et al. 2010 [94]		0.02%		0.02%		
Black et al. 2007 [99]		0.03%		0.03%		
Peng et al. 2022 [24]			ROR:6.5	ROR:1.2		
Bone et al. 2017 [98]					0.30%	
Hallmer et al. 2018 [97]			0.04%			

BPs: Bisphosphonates; ROR: Reporting Odds Ratio; y: year

for prostate cancer, and 4.0% for other neoplasms) [87]. However, the median number of treatment cycles and time of exposure to bisphosphonates were significantly higher for patients with ONJ (35 infusions and 39.3 months, respectively) than in those without ONJ (15 infusions and 19 months, respectively), while the duration of bisphosphonate exposure also increased the incidence of ONJ, from 1.5% in patients treated for 4 to 12 months to 7.7% in those treated for 37 to 48 months [87]. Data from the retrospective pharmacovigilance study of FAERS database revealed for cancer-related indications, median onset time for ONJ was 680.5, 488, and 696.5 days for zoledronic acid, denosumab, and pamidronate, respectively [24]. The onset time of ONJ, which may not be related to the indications, was about 2 years for bisphosphonates, 1.3 years for denosumab and less than 1 year for romosozumab, possibly due to sequential usage [24]. Also, the cumulative hazard of developing ONJ was found to be significantly higher in multiple myeloma patients treated with zoledronic acid alone (1% at 1 year and 15% at 4 years) than in those treated with treated with pamidronate or sequentially with pamidronate and zoledronate or with zoledronate and ibandronate (0% at 1 year and 5% at 4 years) [85]. In a study with 904 myeloma patients (71% on zoledronic acid, and 29% on pamidronate), at 36 months censure of data, rate of ONJ was noted to develop in 10% of patients receiving zoledronic acid, compared with 4% of patients receiving pamidronate, and the mean time to the onset of ONJ was 18 months in zoledronic acid-treated patients, as compared with 6 years in pamidronate-treated patients [86]. The cumulative hazard of developing ONJ was also reported to be significantly higher with exposure to zoledronic acid compared with pamidronate alone or sequential pamidronate and zoledronic acid [87]. In a series of 143 patients with documented ONJ, the median time to development of ONJ with the use of oral bisphosphonates, pamidronate and zoledronate was 54, 34 and 16 months respectively [102]. Hence, the

risk of development of ONJ is considered to vary according to the type of bisphosphonate and duration of exposure, with more potent agents increasing the risk with shorter durations of exposure [103].

Zoledronate and denosumab in cancer patients: Among cancer patients (n=5,723), the risk of developing MRONJ at 1, 2 and 3 years was reported to be 0.5%, 1.0% and 1.3% for those exposed to zoledronate, and to be 0.8%, 1.8% and 1.8% for those exposed to denosumab, respectively [104]. In a pooled analysis of three-blinded phase III trials, similar results were found including a plateau after 2 years for patients exposed to denosumab [90]. In a recent systematic review, the risk of MRONJ among cancer patients treated less than 2 years and more than 2 years were 1.0-4.0% and 3.8-18.0% respectively for patients exposed to zoledronate, and were 1.9% and 6.9%, respectively for those exposed to denosumab [105]. In a phase III study on the efficacy and safety of denosumab compared with zoledronic acid in delaying bone complications in patients newly diagnosed with multiple myeloma, the patient–year adjusted incidence of positively adjudicated MRONJ at the end of the double-blind treatment phase was 2% during the first year of treatment, 5% in the second year, and 4.5% per year thereafter [74]. In a risk–benefit analysis of denosumab versus zoledronic acid on the basis of combined data from 5723 patients with bone metastases, the authors noted that 212 patients and 7 patients need to be treated with denosumab for 1 year to incur 1 more event of MRONJ and to prevent one additional SRE, compared with zoledronic acid, respectively [90].

Treatments in osteoporosis patients: For patients receiving bisphosphonate therapy to manage osteoporosis, early data from retrospective studies indicated an increasing prevalence of MRONJ over time from almost 0% at baseline to 0.21% after ≥4 years of exposure [5,106]. However, the extension of the HORIZON Pivotal Fracture trial for up to 6 years resulted in one additional MRONJ patient (0.03%) to the 3-year (0.03%) results in the treatment group and extension to 9 years resulted in no additional confirmed cases of MRONJ [107,108]. Hence, given that no significant increase in MRONJ in patients treated for up to 9 years, along with no post-marketing data or general clinical experience to support an MRONJ prevalence of 0.21% in any osteoporosis-treated group, it is considered that while duration may be a risk factor, the overall risk remains low [5,107,108]. Data from the retrospective pharmacovigilance study of FAERS database revealed for osteoporosis-related indications, the onset time for ONJ was about 2 years for zoledronic acid, ibandronate, and risedronate, about 1.3 years for denosumab, and 0.5 years for romosozumab, similar to cancer-related indications [24]. Overall, the benefit provided by antiresorptive therapy is considered to outweigh the risk of development of MRONJ (by a factor of 17) in the both osteoporosis and oncology settings [12,33,34,54].

Bisphosphonate Therapy after Development of ONJ

Given the introduction of newer and more potent bisphosphonates (i.e., zoledronate after pamidronate) and denosumab, treatment switch from one antiresorptive drug to another is considered very likely for several patients [109,110]. As bisphosphonates are not metabolized and continue to maintain high concentrations within bone for long periods of time, the transition in antiresorptive therapy may have an additional risk for development of MRONJ due to cumulative osteoclast suppression from both drugs [111]. However, it is unclear if altering the dose, schedule or type of bisphosphonate affects the symptomatic complication rate of ONJ [103]. Previous studies reported a wide variance in MRONJ prevalence for sequential therapy with pamidronate and zoledronate (2% to 52% in retrospective studies, 9% to 36% in prospective studies), for pamidronate only (0% to 18% and 1% to 50%, respectively) and for zoledronate only (1% to 13% and 7% to 25%, respectively) [81,82,85,87,111-116]. Some authors suggested that when bisphosphonate therapy is to be resumed post development of ONJ, it may be prudent to use pamidronate in lieu of zoledronate and also to administer it at less frequent intervals than the standard monthly infusions [103]. Notably, in a systematic review and meta-analysis of 12 studies on the prevalence of MRONJ in patients treated with sequential antiresorptive drugs, a weighted pooled MRONJ prevalence was found to be 19% for sequential pamidronate-zoledronate therapy (median time to ONJ: 9.4 to 127 months), 10% for sequential ibandronate-zoledronate therapy (median time to ONJ: 7.5 to 89 months) and 13% for sequential bisphosphonate-denosumab therapy (median time to ONJ: 25 months) [72,87,111,113,114]. Hence, an increased prevalence of MRONJ is noted with sequential pamidronate-zoledronate therapy when compared to only pamidronate or only zoledronate drug administration, along with a higher prevalence of MRONJ in patients who were transitioned from bisphosphonates to denosumab, compared to patients who only received either bisphosphonates or denosumab [111]. In addition, authors also noted a higher unweighted prevalence of MRONJ amongst patients with multiple myeloma, possibly due to greater cumulative doses or longer period of antiresorptive therapy administered when compared to patients with bone metastasis from other malignancies [111,115]. In the setting of post development of ONJ, it becomes important to determine the potential risk of further osteonecrosis versus the risk of skeletal complications or hypercalcemia of malignancy [117]. However, since bisphosphonates are incorporated into the bone mineral matrix, it remains unknown whether stopping bisphosphonate therapy provides benefit for managing ONJ, while altering the patient's bisphosphonate regime, such as switching from a nitrogen containing to a non-nitrogen containing bisphosphonate, is also suggested a potential strategy besides the discontinuation of bisphosphonates [117-119]. Nonetheless, there are no universally accepted treatment protocols regarding the best strategy to be followed in post development of ONJ, with no evidence available to recommend discontinuation, maintenance or temporary withdrawal of bisphosphonate therapy once ONJ has developed [111]. Hence, treatment switch is mainly based on the careful evaluation of risk/benefit assessment on an individualized basis and avoiding the sequential antiresorptive treatment when possible [103,111].

Conclusion

BON is a rare but potentially serious adverse event of bisphosphonates, specifically in the oncology setting with high-dose/long-term use of bisphosphonates. Although pamidronate seems to be associated with a much lower risk and a later onset of ONJ than zoledronate, possibly due to its less potent inhibitory effect on bone turnover and a weaker anti-resorptive activity, the dose and duration of bisphosphonate is considered a major risk factor for the BON development, with more potent agents increasing the risk with shorter durations of exposure. A timely diagnosis of BON, which necessitates a high index of suspicion and sufficient awareness of the clinician, is important along with a personalized conservative or surgical treatment plan in affected patients. In fact, minimizing the risk of BON via preventive measures is even more critical given that the benefits of antiresorptive therapy far outweigh the potential risks. In this regard,

it should be ensured that both osteoporotic and oncologic patients are well informed about the potential risks and considerable benefits of antiresorptive therapy as well as the effectiveness of preventive measures in substantial risk control. Future studies are needed to better understand the multifactorial ONJ pathophysiology, disease prognosis and outcomes, to determine predictors for increased risk of BON or prognostic indicators predictive of outcomes and to enable further validation of the proposed potential therapeutical approaches.

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