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Review

Medication-related osteonecrosis of the jaw: A literature review

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ABSTRACT

Background: Antiresorptive agents such as bisphosphonates and denosumab, as well as angiogenesis inhibitors, may induce medication-related osteonecrosis of the jaw (MRONJ). However, the exact mechanisms of MRONJ are unclear and definitive treatment strategies have not yet been developed. Moreover, the aging population requiring antiresorptive agents and angiogenesis inhibitors has been increasing worldwide. Therefore, the aim of this literature review was to introduce the latest information on MRONJ. The epidemiology, triggering factors, risk factors, drug holiday, pathoetiology and treatment strategies for each drug-induced ONJ were investigated by conducting a PubMed search.

Highlight: The prevalence and incidence of ONJ were very low. Some mechanisms of ONJ have been identified, although they were not definitive. Novel treatment strategies have been proposed in basic and clinical research. Several factors, including age and the administration duration of bisphosphonates, are risks for the development of bisphosphonate-related ONJ (BRONJ). Dental implant therapy and peri-implantitis could become risk factors of BRONJ, regardless of the onset timing of bisphosphonates. No reliable information about ONJ induced by denosumab and angiogenesis inhibitors was found.

Conclusion: Caution should be taken when dental treatment including implant therapy is performed in patients receiving bisphosphonates, denosumab, and angiogenesis inhibitors. There is limited scientific evidence regarding the relationship between MRONJ and older age. Further ONJ-related research on the aging population is required to manage the treatment of such diseases in older people in the future.

Contents

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1. Introduction

Antiresorptive agents such as bisphosphonates and denosumab, strongly suppress osteoclast activities, although the molecular modes of action are rather different among these drugs. Bisphosphonates, which have a high affinity to hydroxyapatites, are taken in by osteoclasts on bone surfaces when osteoclasts resorb bone. These bisphosphonates induce osteoclast apoptosis via the mevalonate pathway [1]. As a result, bone formation outmatches bone resorption due to unbalanced osteoblasts/osteoclasts on the bone surface [1]. In contrast, denosumab, a monoclonal anti-receptor activator of nuclear factor kappa B ligand (RANKL) antibody, mainly suppresses osteoclast survival and differentiation via the inhibition of binding of RANKL to RANK [2]. Both antiresorptive agents are commonly used in patients with osteoporosis to prevent bone fractures. In 2010, an estimated approximately 99 million older people (>50 years of age) were diagnosed with osteoporosis in the United States [3]. Hip fractures due to osteoporosis can increase the number of bedridden older people, affecting their quality of life and function and leading to a high risk of death at one year after hip fracture [4]. Bone fractures also generate an enormous financial burden on the country. For instance, by the year 2040, the estimated annual health care costs will reach 9.8 billion dollars in the United States [4]. Therefore, antiresorptive agents are requisite for both treating osteoporosis and reducing national costs, although other drugs including parathyroid hormone (PTH), activated vitamin D3, vitamin K12, calcium intake, and selective estrogen receptor modulators, can be administered as therapeutic drugs depending on the clinical symptoms and bone mineral density. Moreover, in 2016, approximately 1,680,000 and 590,000 people were estimated to have been newly diagnosed with or died from cancer in the United States, respectively [5]. Both bisphosphonates and denosumab have been used in cancer patients to suppress hypercalcemia and skeletal-related events. In addition, it has been reported that bisphosphonates reduce the risks of colorectal and breast cancers [6–8]. The overall survival rates in bone metastasis patients or lung cancer patients receiving denosumab are comparable or superior to those in similar patients receiving intravenous bisphosphonate [9,10]. Hence, from the viewpoint of oncological therapies, bisphosphonates and denosumab are absolutely required.

In 2003, bisphosphonate-related osteonecrosis of the jaw (BRONJ) was reported in oncology patients receiving intravenous bisphosphonates [11]. Moreover, in 2010, denosumab-related osteonecrosis of the jaw (DRONJ) was observed [12], although a phase III clinical trial targeting osteoporosis patients reported that DRONJ did not occur after treatment [13]. In addition, the anti-vascular endothelial growth factor (VEGF) agent bevacizumab has been also reported to induce ONJ. VEGF plays a critical role in angiogenesis. Therefore, the term medication-related ONJ (MRONJ) has been proposed instead of BRONJ and/or DRONJ by the American Association of Oral and Maxillofacial Surgeons (AAOMS) [14]. More recently, a phase III clinical trial demonstrated that the anti-sclerostin antibody romosozumab induces ONJ [15]. Clinical and basic research regarding MRONJ has been performed to clarify the exact mechanisms of MRONJ. However, the reasons why MRONJ occurs in patients taking antiresorptive agents and angiogenesis inhibitors remain unknown. Moreover, definitive treatment strategies have not yet been developed due to these unclarified mechanisms.

The number of older people aged >65 years, has increased worldwide because of prolonged average lifetimes and decreased birth rates [16]. Consequently, the rise in the number of older people is likely to increase the number of patients with osteoporosis and cancer, which furtherer increases the use of antiresorptive agents and angiogenesis inhibitors and is a risk for also increasing the number of MRONJ patients worldwide. Therefore, both researchers and health care providers should be aware of the relationship between MRONJ and older age. They also need to have the knowledge of each drug-induced ONJ since the modes of action are quite different among drugs.

The aim of this literature review was to provide the latest information about MRONJ including our findings from basic and clinical research.

2. Epidemiology (Table 1)

2.1. Prevalence of ONJ in osteoporosis patients taking oral bisphosphonates and subcutaneous denosumab

The prevalence of BRONJ is approximately 0.001% in Canada [17], 0.004% in Scotland [18], 0.00038% in Germany [19], and 0%–0.186% in Korea [20]. In contrast, in the United States, the prevalence of BRONJ is 0.1% in osteoporosis patients receiving long-term oral bisphosphonate therapy, which increased to approximately 0.2% in patients taking oral bisphosphonates for longer than 4 years [21]. In summary, the prevalence of BRONJ in patients taking oral bisphosphonates for the treatment of osteoporosis ranges from 0% to 0.04% [22]. No information about the prevalence of DRONJ in patients receiving subcutaneous denosumab therapy was noted.

2.2. Incidence of ONJ in osteoporosis patients taking oral bisphosphonates and subcutaneous denosumab

The incidence of BRONJ in patients taking oral bisphosphonates ranges from 1.04 to 69 per 100,000 patient-years [22]. In contrast, the incidence of DRONJ in osteoporosis patients ranges from 0 to

30.2 per 100,000 patient-years [22]. In summary, the AAOMS concluded that the incidence of ONJ in patients with osteoporosis is very low [22].

2.3. Prevalence of ONJ in cancer patients taking intravenous bisphosphonates, subcutaneous denosumab, and intravenous bevacizumab

The prevalence of BRONJ in patients with malignancies receiving intravenous bisphosphonates is 0%–0.186%. In particular, the prevalence of BRONJ following tooth extraction in cancer patients receiving intravenous zoledronate is estimated to range from 1.6% to 14.8% [17,23], indicating that tooth extraction is the main triggering factor for the development of BRONJ in cancer patients. The incidence of DRONJ in oncology patients receiving subcutaneous denosumab ranges from 0.7% to 1.9%, which was not significantly different from that in intravenous bisphosphonate users [14]. Moreover, the prevalence of ONJ induced by angiogenesis inhibitors such as bevacizumab was approximately 0.2% [14,24]. The prevalence increased to 0.9% when angiogenesis inhibitors were used in combination with bisphosphonates [24].

2.4. Incidence of ONJ in cancer patients taking intravenous bisphosphonates, subcutaneous denosumab, and intravenous bevacizumab

The incidence of BRONJ in oncology patients receiving intravenous bisphosphonate therapies ranges from 0 to 12,222 per 100,000 patient-years [22]. The incidence of DRONJ in patients with malignancies taking subcutaneous denosumab ranges from 0 to 2316 per 100,000 patient-years [22]. Information about the incidence of ONJ induced by angiogenesis inhibitors could not be found in reliable literature such as systematic reviews and/or consensus statements.

3. Triggering and risk factors

3.1. Triggering factors of ONJ

A current systematic review reported that the triggering factors of BRONJ include tooth extraction (61.7%), spontaneous occurrence (14.8%), oral surgery (7.2%), prosthodontic trauma (7.4%), periodontitis (5.0%) and dental implant therapy (3.9%) [25]. Tooth extraction has also been shown to be associated with the development of DRONJ [26]. No detailed information on the triggering factors of DRONJ was found. Similarly, no Information on the triggering factors of ONJ induced by angiogenesis inhibitors have been reported (Table 2).

3.2. Risk factors for ONJ

The reported risk factors for the development of BRONJ include age, administration duration, administration route, type and dose of bisphosphonates, use of steroids or chemotherapies, types of systemic and local diseases, dental procedures, and anatomical. BRONJ occurs significantly more often in older vs. younger people, intravenous vs. oral administration, high-dose vs. low-dose bisphosphonates, zoledronate vs. any other oral bisphosphonates, steroid users vs. non-users, and chemotherapeutic users vs. non-users [14,22,25]. Tooth extraction, dental implant treatment, periodontal surgery, and apicoectomy have been reported to be similar risk factors for the development of BRONJ [14,22,25]. Thinner mucosa (palatine and mandibular tori) and poor oral hygiene have also been reported as risk factors for BRONJ [14,22,25]. Recently, bisphosphonate administration after implant placement [27] and peri-implantitis [28] have been reported to be associated with BRONJ in humans. Therefore, appropriate dental treatment protocols should be established in older people since the number of older people requiring several types of medications, including bisphosphonates and denosumab, with osteoporosis and cancers has been increasing worldwide.

Tooth extraction, chemotherapy, poor oral hygiene and ill-fitting dentures have also been demonstrated to be risk factors for the development of DRONJ [26]. However, information about the risk factors for ONJ induced by angiogenesis inhibitors has not been reported.

Table 1
Prevalence of osteonecrosis of the jaw (ONJ).

Prevalence of ONJ	Bisphosphonates (BPs)	Oral BPs	0~0.04 %
		Intravenous BPs	0~0.186%
	Denosumab	Low dose	N/A
		High dose	0.7~1.9%
	Angiogenesis inhibitors		0.2 %

4. Drug holiday

It remains controversial whether the secession of bisphosphonates, denosumab, and angiogenesis inhibitors is an effective strategy for the prevention or reduction of ONJ.

4.1. Osteoporosis patients receiving antiresorptive therapy

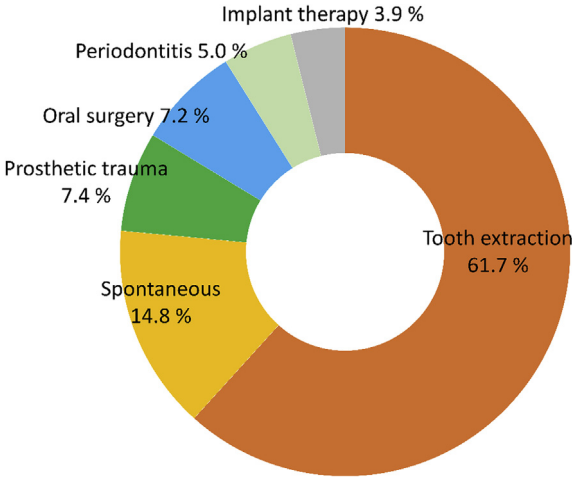
In 2009, the AAOMS position paper on BRONJ recommended discontinuation of oral bisphosphonates for 3 months before and after invasive dental surgery if the patient's systemic condition permits [29]. However, there is no evidence that the secession of oral bisphosphonates prevents or reduces the risk of BRONJ after invasive surgery. Moreover, the half-life of bisphosphonates is longer than 10 years [30]. In 2011, the United States Food and Drug Administration concluded that the discontinuation of oral bisphosphonates was not necessary before dental surgeries [31]. Therefore, the risks and benefits of interrupting oral bisphosphonates should be considered. However, in clinical situations such as extensive oral surgery as well as risk factors of ONJ (systemic or local diseases), the International Task Force on Osteonecrosis of the Jaw recommends discontinuation of antiresorptive therapy if bone health is not disturbed [22].

4.2. Oncology patients receiving antiresorptive therapy

Cancer patients receiving intravenous bisphosphonates and subcutaneous denosumab have greater risks of BRONJ and DRONJ as compared to those in osteoporosis patients taking oral bisphosphonates and subcutaneous denosumab. Hence, discontinuation of intravenous bisphosphonates and subcutaneous denosumab may be considered by oncologists [14,22]. However, data supporting the effectiveness of secession of intravenous bisphosphonates and subcutaneous denosumab on the prevention and reduction of BRONJ and DRONJ are unavailable.

Denosumab is a human antibody with a limited drug efficacy of 6 months. Hence, unlike bisphosphonates, the secession of denosumab may contribute to the prevention and reduction of DRONJ. However, no evidence exists regarding the effectiveness of denosumab discontinuation.

Table 2
Triggering factors of BRONJ.



4.3. Oncology patients receiving angiogenesis inhibitor therapy

To our knowledge, there are no data supporting the effectiveness of the secession of angiogenesis inhibitors for the prevention and management of ONJ. Therefore, the risks and benefits must be considered since patients receiving angiogenesis inhibitor therapy have severe oncologies that affect their life prognosis.

In summary, there is no basic or clinical evidence that the discontinuation of antiresorptive agents and angiogenesis inhibitors prevents and reduces ONJ. Further investigation is required to clarify the secession effects of these drugs on tooth extraction socket healing and ONJ.

5. Pathoetiology (Table 3)

5.1. Pathoetiology of BRONJ

Several mechanisms of BRONJ have been reported. However, the exact mechanisms of BRONJ are unclear, since reliable and available animal ONJ models have not yet been established. The following factors are proposed to be causes of ONJ.

5.1.1. Osteoclast suppression

Antiresorptive agents suppress osteoclast numbers on the bone surface. The process of bone resorption by osteoclasts is requisite for osseous wound healing after invasive surgeries including tooth extraction. Hence, the suppression of osteoclasts could delay and impair osseous wound healing. Animal studies on BRONJ have shown significantly decreased tartrate-resistant acid phosphatase (TRAP) staining of osteoclasts in impaired tooth extraction socket healing, suggesting that a decreased number of osteoclasts is associated with BRONJ in animal studies, including our previous rodent studies [32,33].

Table 3
Pathoetiology of BRONJ and DRONJ.

	BRONJ	DRONJ
Osteoclast suppression	✓	✓
Accumulation of TRAP positive cells	✓	?
Immune alteration (Tregs, Th17)	✓	?
M1 and M2 macrophages	✓	?
Anti-angiogenesis	✓	?
Anti-lymphangiogenesis	✓	?

5.1.2. Immune alteration

Regulatory T cells (Tregs) and inflammatory T-helper-producing interleukin 17 (Th17) cells may contribute to the development of BRONJ-like lesions in mice [34]. Tregs and Th17 were significantly suppressed and activated in BRONJ-like lesions in mice, respectively. Systemic transplantation of mesenchymal stem cells prevented and cured BRONJ-like lesions with suppressed Th17 cells and increased Tregs [34]. Therefore, immune alteration affected by bisphosphonates may be associated with the etiology of BRONJ. Further studies are needed to confirm the relationship between immune alteration and BRONJ.

5.1.3. Unbalanced M1 and M2 macrophages

Our previous study indicated significantly altered M2/M1 macrophage ratio in BRONJ-like lesions after tooth extraction [35]. Another study also observed this alteration in BRONJ-like lesions [36], although the dose and duration of zoledronate differed between these two studies. More recently, it has been demonstrated in mice that zoledronic acid promoted M1 polarization through toll-like receptor-4, which may contribute to the development of BRONJ-like lesions in mice [37]. The ratio of M2 to M1 macrophages is also reportedly reduced in patients with BRONJ [36].

These basic and clinical findings strongly suggest that altered distribution of M1 and M2 macrophages in tooth extraction sockets may be associated with critical mechanisms of BRONJ.

5.1.4. Anti-lymphangiogenesis and anti-angiogenesis

Lymphangiogenesis plays an important role in innate and acquired immune responses. Lymphatic endothelial cells contribute to the recruitment of antigen-presenting cells such as dendritic cells and macrophages into lymph nodes, blocking bacterial infection after dental surgeries. In our previous study, the number of lymphatic vessels and the production of vascular endothelial growth factor C (VEGFC), which is requisite for lymphangiogenesis, were significantly decreased in BRONJ-like lesions when compared to those in normal tooth extraction sockets [33], suggesting that suppressed lymphangiogenesis may be associated with BRONJ.

BRONJ was first described as “avascular necrosis of the jaw” [11]. However, our previous studies in wild-type mice showed that zoledronate monotherapy did not suppress angiogenesis in the connective tissue of tooth extraction sockets [33,38]. Furthermore, zoledronate monotherapy did not induce impaired soft tissue healing of tooth extraction sockets. In a recent study using anti-vascular endothelial growth factor A (VEGFA) monoclonal antibody therapy, we revealed that the inhibition of only anti-angiogenesis does not induce BRONJ-like lesions in mice. Moreover, an international consensus statement supported findings in animal studies that bisphosphonate therapy does not decrease the number of blood vessels [22]. Indeed, histological findings showed normal blood vessel formation in ONJ lesions in humans [39,40], whereas bevacizumab therapy reportedly induced ONJ in oncology patients [24]. Therefore, more basic and clinical studies are required to explore whether inhibition of angiogenesis is essential for the development of ONJ.

5.1.5. Accumulation of TRAP-positive cells

We showed significant increases in nonattached osteoclasts and TRAP-positive mononuclear cells were significantly increased in the connective tissue of tooth extraction sockets treated with zoledronate monotherapy [41] or zoledronate/chemotherapeutic combination therapy [35]. Moreover, transplantation of non-cultured stromal vascular cells significantly decreased the

number of these cells, with a reduction of BRONJ-like lesions [35]. Clinically, nonattached osteoclasts were significantly increased in patients taking oral and intravenous bisphosphonates [42,43]. Hence, the accumulation of TRAP-positive cells including nonattached osteoclasts and TRAP-positive mononuclear cells in extraction wounds may be associated with the development of BRONJ.

5.2. Pathoetiology of DRONJ

As mentioned above, BRONJ-animal models are well established. However, reliable DRONJ-animal models [44] have rarely been developed since denosumab is ineffective in rodents. A recent study demonstrated the development of anti-RANKL antibody in rodents, which resulted in long bone gain by osteoclast suppression [45]. We also demonstrated delayed healing occurs in palatal wounds of mice that received subcutaneous anti-RANKL monoclonal antibody therapy [46]. The creation of reliable and available anti-RANKL antibody-induced ONJ-like lesions is required to investigate the effects of anti-RANKL antibody on tooth extraction socket healing.

5.3. Pathoetiology of ONJ induced by angiogenesis inhibitors

No information about the pathoetiology of ONJ induced by angiogenesis inhibitors was noted.

6. Treatment strategies

We demonstrated that the intermittent administration of PTH significantly reduced BRONJ-like lesions in rats [47]. Intermittent PTH administration also healed BRONJ in clinical study [48]. However, MRONJ frequently occurs in oncology patients and the administration of PTH administration is restricted in cancer patients.

The AAOMS position paper regarding MRONJ proposed that irrigation, antibiotic therapy, and follow-up observation are mainly recommended in MRONJ patients [14]. However, a recent systematic review indicated that MRONJ was rarely healed even after these recommended strategies [49]. The authors concluded that conservative and extensive surgeries that remove necrotic bone and/or surrounding healthy bone primarily healed MRONJ. A recent multicenter clinical study also indicated that surgeries to resect necrotic bone and/or surrounding healthy bone frequently healed stage 2 MRONJ, although these surgical approaches did not heal all MRONJ [50]. Therefore, new alternative treatment strategies to PTH therapy and surgical approaches are required.

In basic research regarding BRONJ, the systemic infusion of bone marrow mesenchymal stem cells has been shown to cure BRONJ-like lesions in mice [34,51]. Moreover, the systemic transplantation of stromal vascular fraction cells of adipose tissue also reduced BRONJ-like lesions in mice [35]. Therefore, cell-based therapies may become a treatment strategy for MRONJ. Conversely, laser therapy [52] and autologous platelet concentrate application [53] have been reported as treatments for MRONJ in humans. However, caution should be taken when MRONJ therapy is performed using laser or autologous platelet concentrate products as there is insufficient clinical evidence to strongly recommend these approaches.

7. Conclusions

MRONJ rarely occurs in patients receiving antiresorptive agents and angiogenesis inhibitor therapies. However, the exact mechanisms of MRONJ have not yet been elucidated. Definitive treatment strategies have also not been developed. Older age is a risk factor for BRONJ, although information about DRONJ and angiogenesis inhibitor-induced ONJ in older people was not found. To manage MRONJ in increasingly aging populations, further basic and clinical research on the relationship between older age and MRONJ is required. Clinical evidence of the relationship between MRONJ and implant therapy in older patients receiving antiresorptive agents and angiogenesis inhibitors should also be accumulated.

Ethical approval

Ethical approval is not required for this review.

Conflict of interest

All authors state that they have no conflict of interest.

CRediTx authorship contribution statement

Shinichiro Kuroshima: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing - original draft, Writing - review & editing. **Muneteru Sasaki:** Data curation, Investigation, Methodology, Visualization, Writing - original draft. **Takashi Sawase:** Conceptualization, Supervision, Writing -review & editing.

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