Oral Science International 10 (2013) 1–8

Contents lists available at SciVerse ScienceDirect

Oral Science International

journal homepage: www.elsevier.com/locate/osi

Review

Pathophysiology of BRONJ: Drug-related osteoclastic disease of the jaw

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ARTICLE INFO

Article history:
Received 27 February 2012
Received in revised form 21 March 2012
Accepted 22 March 2012

Keywords:
Osteonecrosis
Bisphosphonate
Osteoclast
Mevalonate

ABSTRACT

Since the first article about bisphosphonate-related osteonecrosis of the jaw (BRONJ) was published in 2003, clinical and basic research for BRONJ has continued worldwide to understand this novel disease. Several organizations have proposed the definition, diagnostic criteria, risk factors, and treatment strategy for BRONJ. Recently, some new drugs used for cancer patients such as bevacizumab and sunitinib have also been reported to be involved in osteonecrosis of the jaw (ONJ). Because ONJ appears to be initially derived from osteoclast inhibition, a new category of diseases named as "drug-related osteoclastic disease of the jaw" may be assumed. Considering the accumulated knowledge related to BRONJ, including osteoclast biology, bisphosphonate pharmacology, animal experiments, and clinicopathological findings, a perspective of BRONJ from the pathophysiological viewpoint is proposed in this review.

Contents

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1348-8643/$ – see front matter
http://dx.doi.org/10.1016/S1348-8643(12)00045-6

1. Introduction

The number of the patients with bisphosphonate-related osteonecrosis of the jaw (BRONJ) has increased year by year since Marx first reported cases of osteonecrosis of the jaw (ONJ) occurring in patients with multiple myeloma treated with intravenously administered bisphosphonate in 2003 [1]. The disease concept of BRONJ seems to be established now since many articles and reviews about BRONJ have been published.

Bisphosphonate (BP) was originally developed as a drug to treat bone resorbing diseases such as multiple myeloma and bone metastasis, whose typical origins are breast cancer and prostate cancer, as well as tumor-related hypercalcemia, and then used for the patients with osteoporosis to prevent their pathological fracture. In Japan, approximately 3 million patients have received BP therapy. A specific target cell of BP is osteoclast which plays a central role in physiological and pathological bone resorption.

Since BP possesses a pyrophosphate-like structure, whose hydroxyl group confers a strong affinity to the hydroxyapatite, 80% of BP administered intravenously or orally deposits to the bones. The half life of BP in humans, which is poorly metabolized by biological enzymes, is thought to be about 10 years, and thus BP may be enriched in the bones, to where osteoclasts, which differentiate from bone marrow stem cells, migrate and adhere to function. That is why BP was expected to work selectively on osteoclasts without adverse effects. Nitrogen-containing BP (nBP) has more potent ability to inhibit mineral dissolution and higher potency to induce BRONJ than early BP without nitrogen-containing side-chain [2]. In this review, "BP" occasionally indicates both nBP and early BP.

Like BP, denosumab, which is anti-human RANK ligand (RANKL) monoclonal antibody and developed to inhibit osteoclasts for the treatment of bone-resorbing diseases, is also suspected to be involved in the occurrence of ONJ that is similar to BRONJ [3,4]. The symptoms seen in chronic osteomyelitis of the jaw occurring in the patients with osteopetrosis, in which osteoclast functions are inhibited by a genetic mutation, also seem to be similar to those of BRONJ. Since these lesions appear to be derived from osteoclast inhibition, we could classify them into a new category of diseases presumably named as "drug-related osteoclastic disease of the jaw". This idea is based on the concept that the "osteoclast is a self-defense regulator of the jaw." The defense mechanism of the jaw should be impaired in the lack of osteoclasts, which is liken to that we become susceptible to infection when our immune cells are inhibited. In this review, hence, the clinical as well as pathophysiological aspects of BRONJ will be discussed according to this concept.

2. Incidence of and risk factors for BRONJ

2.1. Incidence

The incidence of BRONJ in the early USA report was 0.8–12% with intravenous BP and 0.7/100,000 (0.0007%) person-years of exposure with oral BP [5]. In Europe, the incidence was 95/100,000 (0.095%) person-years of exposure with intravenous administration and 1/100,000 (0.001%) person-years of exposure with oral administration [6]. BRONJ occurred in 1.15% of intravenously administered patients and in 0.04% of the orally administered patients in Australia [7]. Another report from the USA indicated that the incidence of BRONJ was 0.1% with oral BP administration [8]. Taken together, these reports suggest that the incidence of BRONJ with oral BP is 0.01–0.1%.

Most of the patients taking oral BP have osteoporosis. Approximately 20% of the 10 million osteoporosis patients in Japan are thought to be treated with medication including BPs. As the elderly population increases, the number of osteoporosis patients taking oral BP will increase and the period for BP administration will prolong, which will result in an increased incidence of BRONJ. Actually, a nationwide retrospective cohort study with a questionnaire on BRONJ in Japan, which was undertaken by the Japanese Society of Oral and Maxillofacial Surgeons, demonstrated that 263 cases of BRONJ occurred in the entry hospitals from 2006 to 2008, and 39.5% of them were patients taking oral BPs [9].

2.2. Tooth extraction

Among various risk factors, including glucocorticoids (GCs), anti-cancer drugs, alcohol, smoking, and malnutrition, to make patients susceptible to BRONJ, tooth extraction and other surgical procedures to the jaws are most problematic to dentists and oral and maxillofacial surgeons. Tooth extraction raised the incidence of BRONJ about 8-fold, from 0.04% to 0.34% in the oral BP-administered patients and from 1.15% to 9.1% in the intravenous BP-administered patients in Australia [7]. BRONJ occurred in 6% in 66 patients orally taking aledronate after tooth extraction [10]. Tooth extraction was related to 77% of BRONJ cases occurring in the patients into whom BP were administered intravenously [11]. Surgical damage to the jaw, especially alveolar bone, is likely to be the most potent trigger to BRONJ while the immunosuppressive agents such as GCs and anti-cancer drugs, could lower the threshold for its occurrence.

Without any risk factors, BRONJ is known to occur spontaneously. The lingual side of the alveolus in mandible is a predisposed site for spontaneous BRONJ, which is thought to be triggered by an injury on the mucosa. Likewise, bony prominence seen in palatal torus and mandibular torus is also susceptible to BRONJ.

2.3. Glucocorticoids

The use of GCs with BP is known to raise the risk for BRONJ because GCs suppress the activities of inflammatory cells and immune cells to make the patients immunocompromized. Since GCs not only activate the osteoclasts, but also inhibit the osteoblasts, the long-term use of GCs induce osteoporosis. That is why patients undergoing GC therapy are also administered BP to prevent osteoporosis. Rheumatoid arthritis (RA) is a typical disease treated both with BP and GCs. Some of the patients with RA are also treated with methotrexate (MTX) together with BP and GC. MTX is a folic acid antagonist and used as an anti-cancer drug as well as anti-rheumatic drug by inhibiting the inflammatory cells and decreasing various cytokine productions, which is likely to increase the risk of BRONJ. RA patients should be paid special attention for preventing BRONJ.

3. Diagnostic criteria and stage classification of BRONJ

3.1. Criteria and stage

In 2007, criteria to diagnose BRONJ were provided in a position paper by the American Association of Oral and Maxillofacial Surgeons as follows: (1) current or previous treatment with a BP; (2) exposed bone in the maxillofacial region that has persisted for more than 8 weeks; and (3) no history of radiation therapy to the jaws [5]. Although an exposure of necrotic bone, sequester, in the jaw is the most prominent characteristic of BRONJ, it is occasionally observed in chronic suppurative osteomyelitis of the jaw. That seems to be a reason why the criteria include the second point. The criterion (3) is to exclude the possibility of osteoradionecrosis of the jaw.

The position paper in 2007 also proposed a staging classification of BRONJ, stage 1, stage 2, and stage 3. Stage 1 shows only an exposure of the bone without infectious signs. Stage 2 includes not

Table 1
Comparison of the level between jaw inflammation and bisphosphonate-related osteonecrosis of the jaw (BRONJ).

Category	Level of the lesion	
	Alveolus	Jaw body
Ostitis	Alveolar ostitis Periodontitis	Periostitis
Abscess	Gingival abscess Alveolar abscess	Subperiosteal abscess
BRONJ	Stage 2	Stage 3

only a bone exposure, but also inflammatory symptoms by bacterial infection such as pain and swelling. The extent of the lesion in stage 2 is limited in the alveolar bone. When the lesion extends to the jaw itself beyond the alveolar level, then, it will be classified to stage 3, where the bone necrosis or osteolysis may extend to the inferior border of mandible with or without extraoral fistula and pathological fracture. The difference between stage 2 and stage 3 will be similar to that between periodontitis and periostitis, depending on the affected area (Table 1).

3.2. Stage 0

All the stages of BRONJ require an exposed bone as a definition. However, it is known that there have been patients taking oral BP who have no bone exposure in the jaw, but suffered from some nonspecific and refractory symptoms such as diffuse alveolar swelling, gingival redness, or internal dental fistula whose origins are not identified. These symptoms have occasionally subsided after the discontinuation of BP therapy. The American Association of Oral and Maxillofacial Surgeons position paper in 2009 added a stage 0 into the BRONJ staging for the cases with no clinical evidence of necrotic bone, but nonspecific clinical findings and symptoms [12]. Fig. 1 shows a plausible explanation about the development of stage 0. In stage 0, an open alveolar socket may persist after tooth extraction, where the surface of the socket is concealed with granulation tissues, but the most part of the bare socket is left behind with a bony surface, presumably because the thickened lamina dura [13], which cannot be resorbed by BP, may prevent the inflammatory cells from infiltrating, impair the wound healing processes, and allow the infection to persist (Fig. 1).

4. Relationship between stage 0 and suppurative osteomyelitis of the jaw

Dentists or oral and maxillofacial surgeons may diagnose the patients with stage 0 simply as suppurative periostitis or osteomyelitis of the jaw, being unaware of their BP administration. If stage 0 lesion is a precursor of BRONJ, bacterial infection may play a critical role in the initiation of BRONJ.

Kos et al. [14] reported that when patients with osteomyelitis of the jaws were divided into two groups, the ones undergoing BP treatment and the others taking no BP, *Actinomyces* was significantly detected on the exposed necrotic bones in the BP-administered patients, suggesting the involvement of *Actinomyces* in BRONJ. Ganguli et al. [15] suggest the affinity of bacteria to BP by showing increased adhesion of *Staphylococcus aureus* to hydroxyapatite in joint prostheses coated with pamidronate. On the other hand, Hansen et al. [16] also detected *Actinomyces* in the necrotic bones of BRONJ as well as osteoradionecrosis in an equally high frequency. Both necrotic bones from BRONJ and suppurative osteomyelitis of the jaws were found to be covered with the bacterial biofilms, but, *Actinomyces* predominated in the biofilm from suppurative osteomyelitis while the biofilm from BRONJ included more diverse bacterial organisms in addition to fungal organisms not observed in suppurative osteomyelitis [17]. Although it remains unknown whether bacterial infections including *Actinomyces* occur primarily or secondarily in the BRONJ process, infection is likely to worsen the symptoms of BRONJ. Thus, BRONJ stage 0 should be initially treated with antibacterial mouth rinse and antibiotics.

As mentioned below, BP inhibits the growth of vascular endothelial cells and impairs the angiogenesis in bone and periosteum. The decrease in blood supply may lead to avascular necrosis of the jaw in BRONJ, which is like osteoradionecrosis of the jaws. But, it is unlikely that avascular and aseptic necrosis of the bones is a primary cause of BRONJ since some infectious lesions such as gingival abscess often precede the development of BRONJ in many cases [18], and stage 0 of BRONJ usually shows some infection signs. Saia et al. [19] reported that among 60 cases of tooth extraction under BP treatment, BRONJ occurred in 3 cases within 3 months, suggesting that suppurative osteomyelitis might be the most influential risk factor to bring out BRONJ.

Regardless of whether bacterial infection causes BRONJ or not, it is important to find out the cases of stage 0 as early as possible and prevent them from progressing to the later stages. Hutchinson et al. found the radiographic features with panoramic radiography and computed tomography (CT), including diffuse osteosclerosis,

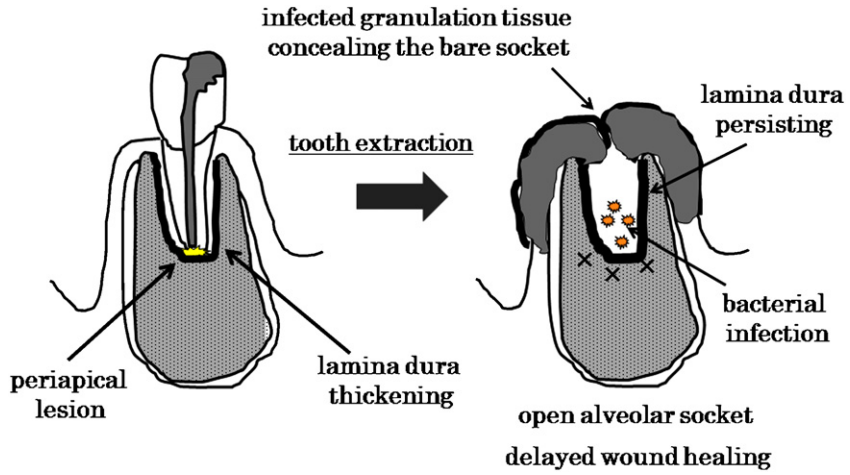

Fig. 1. What happens in the jaw of Stage 0? Thickened lamina dura will prevent white blood cells from infiltrating and granulation tissue from forming in the socket, resulting in delayed wound healing and persistent infection.

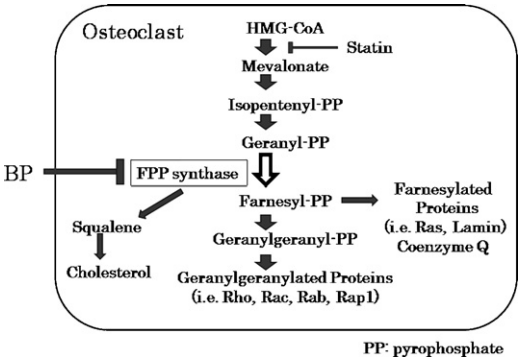

Fig. 2. Bisphosphonate (BP) targeting the mevalonate pathway. FPP, farnesyl diphosphate; PP, pyrophosphate.

thickened lamina dura, prominence of the inferior alveolar canal, and cortical disruption, in 10 cases among 30 patients with stage 0 [20]. In my opinion, hence, CT or cone beam CT seems to be useful to detect these initial changes in the bones for the early diagnosis of stage 0.

5. Mechanism of nitrogen-containing BP actions

The molecular target of nBP is a farnesyl diphosphate synthase (FPP synthase) in osteoclasts [2,21,22]. At first, nBP was supposed to inhibit the mineral dissolution by its binding to mineral components outside osteoclasts, but now it is known that nBP enters into the osteoclasts to inhibit the activity of FPP synthase which is an enzyme involved in mevalonate pathway of osteoclasts (Fig. 2). This effect of nBP was found in the research for an agent to lower the level of serum cholesterol which is synthesized through mevalonate pathway [2]. FPP synthase is an enzyme to convert geranyl diphosphate to farnesyl diphosphate, which is in turn converted to geranylgeranyl diphosphate. Geranylgeranyl diphosphate activates the small GTPases, such as Rab, Rac, Ras, and Rho, through their isoprenylation and geranylgeranylation. Small GTPases then regulate the cytoskeletal arrangement, vesicular trafficking, and membrane ruffling which are involved in the processes of bone resorption by osteoclasts, including their migration to bones, adhesion on bone surface and transportation of bone-resorbing enzymes to the ruffled border. Therefore, the inhibition of FPP synthase with nBP can prevent osteoclasts from destructing the bones (Fig. 2).

There may be evidence to show that nBP disturbs the cytoskeletal regulation. Weinstein et al. observed the osteoclasts in the bone-biopsy specimens of iliac bone obtained from healthy postmenopausal women receiving 3-year oral alendronate therapy, compared with the placebo-controlled ones in a doubled-blind, randomized trial [23]. In theory, it was expected that there would be few osteoclasts in the bones from the patients taking nBP. Surprisingly, however, the number of the abnormal osteoclasts, which were giant, hypernucleated (with 20–40 nuclei), detached from bone surface, increased as the cumulative dose of alendronate increased. Of these giant osteoclasts, 20–37% were apoptotic. They suggest that nBP protracts the apoptosis of osteoclasts, where cell fusion continues to generate the distinctive morphology such as giantism and hypernucleation. These features may be attributed to nBP-mediated loss of small GTPase.

Such an increase in the number of giant, hypernucleated osteoclasts is also observed in the bones from patients with Schönberg disease or autosomal dominant osteopetrosis type II, in which the ability of osteoclasts to decay bone is impaired because of the mutations in *CLCN7* gene encoding a chloride channel [24]. nBP may inhibit the function of CLCN7 [25]. Hansen et al. [16] also found many osteoclasts in the necrotic bones from the BRONJ patients administered with pamidronate or zoledronate. These data suggest that nBP brings about the functional disorder, rather than the depletion, of osteoclasts.

6. Other target cells of BP

Although osteoclasts have been thought to be a specific target of nBP, it is difficult to attribute the occurrence of exposed bone necrosis only to osteoclast disorder. Some other cells are thought to take part in establishing BRONJ.

6.1. Osteoblasts

Osteoclasts are known to indirectly assist bone formation, where osteoclastic bone resorption can release some growth factors buried in the bone, which stimulate osteoblasts to make bones [26]. The cooperation of osteoclasts with osteoblasts, which is called “coupling”, is thought to be essential for bone turnover. Thus, the loss of osteoclasts is likely to impair the activity of osteoblasts, resulting in the bone turnover arrest to osteonecrosis. On the other hand, the direct effects of nBP on osteoblasts have also been investigated. Zoledronate inhibited the growth and viability of cultured osteoblasts [27,28], while pamidronate and zoledronate were reported to inhibit the cell growth, but increase the bone formation of immortalized fetal osteoblasts [29]. The damage to osteoblasts may be associated with the occurrence of BRONJ, which hypothesis may be supported by the report that parathyroid hormone might improve the BRONJ by stimulating osteoblasts, as mentioned below.

6.2. Osteocytes

Allen and Burr [30] examined the bone matrix in the mandible from beagle dogs treated with clinically relevant doses of daily oral alendronate for 3 years and found significant amounts of necrotic bone matrix in approximately 25% of nBP-treated animals, which were predominantly present in the alveolar portion of the mandible. The non-viable bone matrix showed empty lacunae without osteocytes. It has been reported that fluorescently labeled risedronate injected intravenously into mice was observed around the lacunae [31]. Because osteocytes are the most abundant bone cells and form an intricate communication network throughout the bone matrix, where osteocytes are thought to provide a signal to osteoclasts to clean up the necrotic bones, the loss of osteocytes may play a role in the pathophysiology of BRONJ [32]. It is likely that the micronecrosis of the bone may accumulate in large amounts because of the lack of osteocyte–osteoclast communication [33,34].

6.3. Vascular endothelial cells

It is assumed that BP inhibits bone angiogenesis by suppressing the growth of vascular endothelial cells to result in avascular necrosis of the bone. There are a number of reports to show that nBP directly inhibits angiogenesis in vitro or in vivo [35,36,28] although the studies on the effects of nBP on angiogenesis in bone marrow and periosteum of the jaw remain to be done [37]. nBP may also exert indirect effects on the suppression of bone angiogenesis since osteoclasts may be required to make vessels pass through bone matrix [38]. This importance of nBP-mediated inhibition of angiogenesis in the jaw could be supported by the reports that the administration of zoledronate reduced the serum levels of vascular endothelial growth factor (VEGF) in patients with bone metastasis [39] and that bevacizumab, an anti-VEGF antibody, may induce osteonecrosis of the jaw [40].

6.4. Keratinocytes

nBP is reported to inhibit the growth of cultured keratinocytes [41]. nBP decreased the number of p63-positive keratinocyte progenitor cells and prevented the gingival fibroblasts from producing keratinocyte growth factor (KGF) [42,43]. It is presumed that inflammation in the jaws, i.e. tooth extraction, releases the nBP buried in the bones, which in turn inhibits the keratinocyte growth to worsen the exposure of bones, especially in patients with an ulcer or an injury formed on the mucosa by unsuitable dentures. The mucosal damage with nBP is demonstrated in a case that the contact of nBP on mucosa induced stomatitis in patients who had the habit to hold the alendronate tablets in the mouth for a while before swallowing them [44,45].

6.5. Macrophages/monocytes

Since osteoclasts differentiate from macrophage/monocyte lineage, it is plausible that nBP inhibits the activity of macrophages. Actually, nBP inhibited the production of cytokines in macrophages and monocytes [31]. The differentiation of dendritic cells, a macrophage lineage, was interfered with by nBP [46,47]. These macrophages/monocytes play an important role in the self-defense system of immunity as antigen-presenting cells. Thus, nBP may suppress the immunological reactions to make bones susceptible to bacterial infection. In this respect, the reason why GC is a risk factor for BRONJ is thought to be attributed to its immunosuppressive action [48,49]. In addition, it is likely that nBP inhibits the differentiation from macrophage/monocyte to osteoclast. Kimachi et al. [50] reported that zoledronate inhibited the tumor necrosis factor-α-induced differentiation of a murine macrophage/monocyte cell line, Raw264.7 to mature osteoclasts.

7. Why does BRONJ occur in the jaws?

It is thought that jaw is the most predisposed to BP-related osteonecrosis because (1) the turnover rate of jaws, especially alveolar bones, is so rapid and (2) jaws have teeth and gum that may become an easy entrance for bacterial infection [51].

7.1. Bone turnover rate

The remodeling rates of the cortical bone in the jaw are 10–20 times higher than in the cortex of iliac crest in humans [52,53]. The level of intracortical bone remodeling in the mandible was found to be more than 10 times higher than in the tibial cortex in dogs, especially, the alveolar portion of the mandible having more than 8 times higher rate of turnover than in the other portions of the mandible [37]. In contrast, some articles show that the turnover of the jaw is not the highest among the bones. Huja and Beck [54] reported that the bone formation rate of the femur is higher than that of the mandible and maxilla in dogs. In athymic rats, the uptake of fluorescently labeled pamidronate to the bones and the release of it per unit calcium were lower in the oral bones than in the axial bones [55]. Apart from the controversy, bone damage such as surgical intervention and infection may accelerate the turnover rate of the jaw.

When fluorescent pamidronate was injected intravenously into mice, 90% of the fluorescent signal localized to bone within 2–6 h of injection, where more signals were detected and retained longer in the mandible rather than in the femur [56]. Moreover, fluorescent pamidronate was found to be deposited in the alveolar bone and bone surrounding the periodontal ligament and molar roots [56]. Taken together, alveolar bone of the mandible is most susceptible to the nBP effects because of rapid turnover rate and high affinity to nBP.

7.2. Vulnerability of the jaw to bacterial infection

Among all the bones, jaw seems to be the most liable to bacterial infection since mucosa covering the alveolar bone is very thin and vulnerable, and teeth easily become a pathway for bacteria from the outside into the bone. Although it is certain that bacterial infection makes BRONJ worse, it remains to be determined whether bacterial infection precedes osteonecrosis of the jaw. Aghaloo et al. [57] found that the necrosis of the alveolar bones developed in the rats, which underwent the placement of a wire ligature around the crown of maxillary molar in a periodontal disease model, after intraperitoneal injection with zoledronate. The necrotic bones were not exposed in these rats whereas the control animals showed the resorption of alveolar bone, but not any osteonecrosis. The results imply that periodontitis, which is presumably infection-related, can trigger the osteonecrosis.

When periodontitis occurs, inflammatory cells are recruited to the sites to eliminate the causative pathogens. However, the blockade of bone resorption with BP may make it difficult for these cells to access to the pathogens, allowing the infection to persist. The resulting accumulation of bacterial toxins and inflammation-generated superoxides will promote the bone necrosis. Thus, bacterial infection is likely to be involved in the formation of BRONJ.

From these assumptions, it seems to be reasonable to treat BRONJ with thorough local rinse and antibiotic administration as a first step to control the infection.

8. Confused effect of nBP on osteomyelitis of the jaw

On the other hand, pamidronate is used to treat patients with chronic non-bacterial osteomyelitis (CNO), including chronic recurrent multifocal osteomyelitis (CRMO), SAPHO (synovitis, acne, pustulosis, hyperostosis, and osteitis), and juvenile diffuse sclerosing osteomyelitis (DSO), which occasionally occur in the jaws [58–61]. Although the causative mechanism of CNO remains unknown, the effectiveness of BP on CNO may rather support the hypothesis that bacterial infection is involved in the initiation of BRONJ. BP can cure non-bacterial osteomyelitis while BP worsens suppurative osteomyelitis to BRONJ.

When dental surgical procedures were applied to 22 patients with osteogenesis imperfecta who underwent BP therapy, no BRONJ cases were observed [62]. It remains unknown why the incidence of BRONJ is so low when BP therapy is applied to osteogenesis imperfecta and CNO.

9. Pathophysiological mechanism of BRONJ

Based on our knowledge as summarized above, the putative mechanism of BRONJ formation is summarized in Fig. 3. After administration, nBPs deposit and accumulate in the alveolar bone, which have a higher turnover rate. During a physiological remodeling of the bone, osteocytes are exposed to the buried nBPs and damaged, leading to the micronecrosis of the bones. The amounts of the necrotic bones gradually increase because osteoclasts cannot degrade the necrotic bones. When tooth extraction is performed, then, the inflammatory cytokines are produced in the periodontal tissues, which exert the serial inflammatory reactions, where the tissue-degrading proteases may be involved in the increased release of nBPs from the alveolar bones. The released nBPs may block angiogenesis and delay the migration of neutrophils, macrophages, and osteoclast progenitors to the site, inhibiting the formation of granulation tissues, which are needed

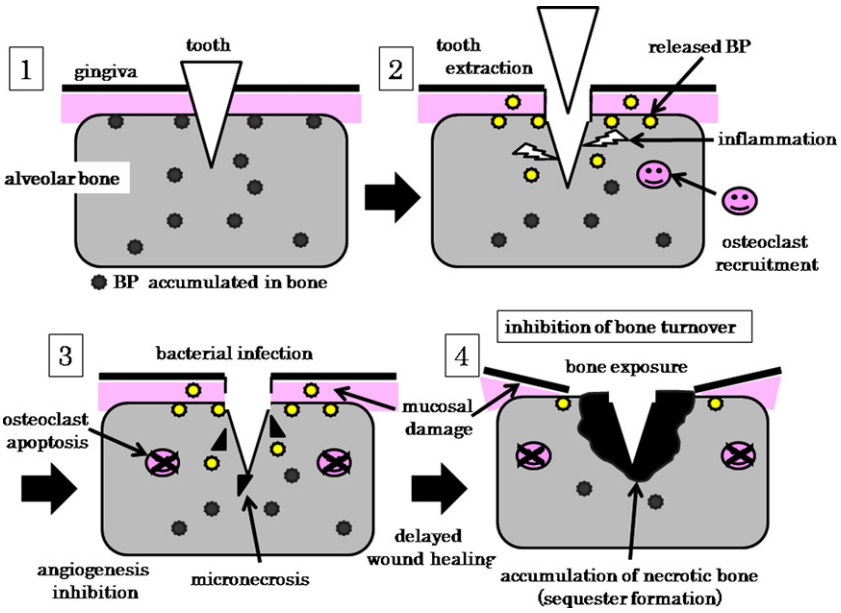

Fig. 3. Hypothesis of pathophysiology of bisphosphonate (BP)-related osteonecrosis of the jaw development.

for wound healing and bone remodeling. The poor vascularity and sequestration in periodontal tissues makes the bacterial infection persist because the recruitment of neutrophils and lymphocytes are blocked. The fistula formation to discharge pus inside bone is also prevented because of the lack of osteoclasts. The persisting infection promotes the increase in osteonecrosis while the uncoupling between osteoblasts and osteoclasts causes the suppression of bone turnover. The released nBPs finally inhibit the proliferation of mucosal keratinocytes, leading to the exposure of necrotic bones.

10. Treatment of BRONJ

The strategies for the treatment of BRONJ have been proposed in the position papers depending on the stages [5,9,12]. BRONJ stage 3 may be treated with a surgical removal of the jaw which contains the necrotic bones while a conservative therapy is indicated for stage 1 or stage 2. One of the basic conservative therapies is a local irrigation with saline or the use of oral antimicrobial rinse.

10.1. Drug holiday

In the patients treated with oral BP therapy, a drug holiday, discontinuation of BP therapy, seems to be effective to restore bone turnover of the jaw and support the treatment of BRONJ. In the position papers, the discontinuation of BP is recommended for more than 3 months before tooth extraction if the patients have received oral BP therapy for more than 3 years. It is expected that bone turnover of the jaw once disturbed with BP will be recovered during a 3-month drug holiday. This concept is supported by the report of Marx et al. [63], where the serum concentrations of CTX, which is a cross-linking peptide of type I collagen, released from the bones during bone resorption and utilized as a marker of bone turnover, were measured in the patients with BRONJ. They found that the serum concentrations of CTX increased from 72.4 pg/ml to 150 pg/ml, which is in the level for low risk of BRONJ, with the discontinuation of BP for 3–4 months. Hence, a 3-month holiday from BP may restore bone turnover of the jaw. In fact, Treister and Woo [64] reported that the mucosa completely covered the exposed bone in stage 2 of BRONJ 4 months after the discontinuation of BP and local rinse. Discontinuation of oral BP therapy is thought to be the first step to care for patients with BRONJ.

It remains controversial whether serum CTX concentration can be used as a predictive marker for BRONJ, because the values of CTX concentration seem to vary from case to case [65,66].

10.2. Hyperbaric oxygen

Since hyperbaric oxygen (HBO) is known to be effective adjunctive therapy for the treatment of chronic osteomyelitis and osteoradionecrosis of the jaw, then, it has also been applied to the treatment of BRONJ. The efficacy of HBO in the treatment of BRONJ has not yet been elucidated, but may be promising because it is expected to improve the hypoxia condition in the jaw and generate reactive oxygen species (ROS) to stimulate the differentiation and activity of osteoclasts [67].

10.3. Teriparatide (recombinant human parathyroid hormone 1–34)

Recently, it has been reported that BRONJ was dramatically improved with teriparatide therapy [68–70]. Teriparatide consists of 1–34 amino acids of recombinant human parathyroid hormone (PTH) (a full PTH includes 84 amino acids), and has been used for the treatment of GC-induced osteoporosis. PTH plays an essential role in the regulation of calcium metabolism. When PTH levels are continuously elevated, bones are severely degraded to increase the serum calcium concentration because of osteoclast activation. In contrast, intermittent pulsatile administration of PTH stimulates the differentiation and function of osteoblasts, rather than osteoclasts, to lead to anabolic effects on bone [71]. Hence, intermittent subcutaneous injection of teriparatide once a day is expected to promote bone formation. In the treatment of BRONJ, teriparatide may cause activation of osteoblasts to restore the bone turnover once inhibited with nBP, and promote the production of receptor activation of nuclear factor-kB ligand (RANKL) from osteoblasts to reactivate osteoclasts.

10.4. Prospective therapy

As mentioned above, nBPs impair osteoclasts through inhibiting FPP synthase in the mevalonate pathway (Fig. 2). If a downstream molecule of farnesyl diphosphate whose generation is mediated

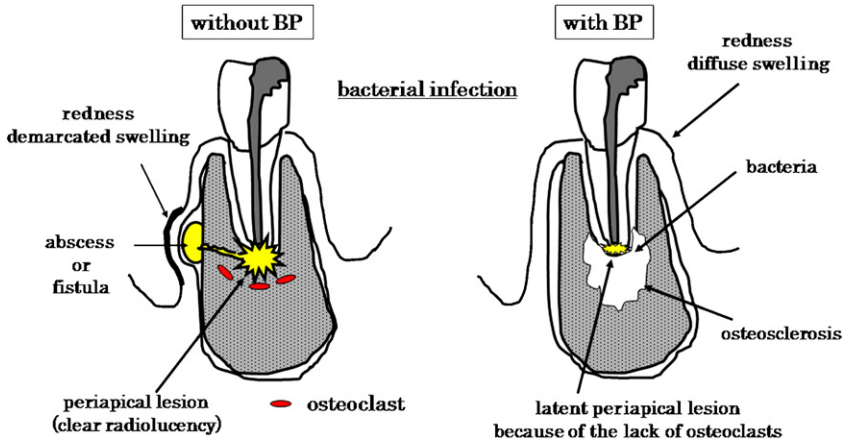

Fig. 4. A role of osteoclasts in self-defense of the jaw. Osteoclasts play an important role in excluding bacteria from the inside of jaw. BP, bisphosphonate.

Table 2
List of the drugs related to osteonecrosis of the jaw.

Drugs related to osteonecrosis of the jaw
Bisphosphonate
Glucocorticoid
Bevacizumab
Denosumab
Sunitinib

with FPP synthase in the mevalonate pathway is supplied into the nBP-treated osteoclasts, the inhibitory effects of nBP on osteoclasts would be compensated. Kimachi et al. [50] found that the addition of geranylgeranyl diphosphate, which is a downstream metabolite of FPP synthase, dramatically restored the motility and RANK expression of the cultured osteoclast precursors which were once inhibited with zoledronate, implying that geranylgeranyl diphosphate neutralizes the effect of nBP. Such an intermediate metabolite in the mevalonate pathway is expected to become a drug to revive the osteoclasts in the patients with BRONJ [72].

11. Drug-related osteoclastic disease of the jaw

Recently, it has been suspected that ONJ is induced not only by nBP, but also by the molecule-targeting drugs, which are newly developed, such as denosumab, anti-RANKL antibody, and bevacizumab, an anti-VEGF antibody [2,40,73]. The number of case reports about ONJ occurring in cancer patients treated with these new anti-cancer drugs appears to be increasing (Table 2). The incidence of ONJ was 0.3–0.4% in the patients with breast cancer undergoing bevacizumab therapy whereas the administration of bevacizumab together with nBP increased the ONJ incidence to 0.9–2.4% [74]. The combination of nBP with sunitinib, which inhibits tyrosine kinase involved in various growth factor receptors to treat renal cell carcinoma, is reported to raise the risk of BRONJ, where sunitinib-induced oral mucositis is thought to trigger the occurrence of BRONJ [75].

According to recent advances in medical science, a number of new drugs have been developed and applied to patients, especially those with cancer. Our society will speed up this situation in the future. On the other hand, the more new drugs are developed, the more adverse effects will emerge. New drugs may induce new diseases such as BRONJ. It is plausible that the jaw is the most vulnerable site to the adverse effects of new drugs because of its special anatomical characteristics. Furthermore, a jaw is composed of a variety of cells, all of which should take part in the life of the jaw. Even damage only to osteoclasts with BP will disturb the network of each cell through the jaw. From this viewpoint, our experiences about BRONJ give birth to a concept that osteoclasts play a critical role in the self-defense of the jaw (Fig. 4). Hence, it suggests that BRONJ or other related jaw disease is newly classified as drug-related osteoclastic disease of the jaw. We should prepare for the challenges from such new diseases.

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