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Review Article

# Medication Related Osteonecrosis of the Jaw: 2015 Position Statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons

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Bisphosphonates are the most widely prescribed drugs for the treatment of osteoporosis, and are also used in malignant bone metastases, multiple myeloma, and Paget's disease, and provide therapeutic efficacy on those diseases. However, it was reported that occurrence of osteonecrosis of the jaw (ONJ) could be related with bisphosphonate exposures, and there have been many cases regarding this issue. Therefore, a clearer definition and treatment guidelines were needed for this disease. The American Society for Bone and Mineral Research (ASBMR) and American Association of Oral and Maxillofacial Surgeons (AAOMS) reported statements on bisphosphonate-related ONJ (BRONJ), and a revised version was recently presented. In the revised edition, the diagnosis BRONJ was changed to medication-related ONJ (MRONJ), which reflects a consideration of the fact that ONJ also occurs for denosumab, a bone resorption inhibitor of the receptor activator of nuclear factor-kappa B ligand (RANKL) antibody family, and bevacizumab, an anti-angiogenesis inhibitor. In 2009, a statement on ONJ was also reported locally by a relevant organization, which has served as basis for clinical treatment in Korea. In addition to the new official stance of the AAOMS and ASBMR, with an increasing pool of ONJ clinical experience, a revised version of the 2009 local statement is needed. As such, the Korean Society for Bone and Mineral Research (KSBMR) and the Korean Association of Oral and Maxillofacial Surgeons (KAOMS) have collectively formed a committee for the preparation of an official statement on MRONJ, and have reviewed recent local and international data to propose guidelines customized for the local Korean situation.

**Key Words:** Bisphosphonate-associated osteonecrosis of the jaw, Bisphosphonates, Osteonecrosis

## MRONJ CASE DEFINITION

In order to differentiate medication-related osteonecrosis of the jaw (MRONJ) from other cases in which treatment is delayed due to other causes, MRONJ is defined according to the following three conditions.

1. Current or past use of antiresorptive or antiangiogenic agents
2. Exposure of the jaw bone or intraoral or extraoral fistula persisting for more than 8 weeks
3. No history of head and neck radiation therapy

## EPIDEMIOLOGY

### 1. Prevalence

The prevalence of osteonecrosis of the jaw (ONJ) in osteoporosis patients who have used bisphosphonates is known to be 0% to 0.04%, and most reports show a low prevalence of less than 0.001%.[1-4] According to a joint study done by 15 hospitals in Korea with a total of 254 cases of ONJ, in 2008, based on 600,000 patients who were prescribed with bisphosphonates, the frequency of bisphosphonate-related ONJ (BRONJ) was estimated to be 0.04% (1 in 2,300), but these results need to be updated with a follow up study.[5] The average age of patients was 70 years old (38 to 88 years old), and 21.8% were due to the intravenous bisphosphonates.[5] The prevalence was reported to be 0% to 0.186% for patients with bone metastases who have been treated with high dose bisphosphonates.[6-8]

### 2. Incidence

#### 1) Incidence in osteoporosis patients

**(1) *Oral bisphosphonates***

In patients administered oral bisphosphonates for the treatment of osteoporosis, the incidence was 1.04 to 1.69 per 100,000 patient-years, showing a great variability among the investigators.[2,3,9]

**(2) *Intravenous bisphosphonates***

The incidence of ONJ when using intravenous bisphosphonates has been reported to be 0 to 90 per 100,000 patient-years.[10-12] In a clinical trial that administered zoledronate as a treatment for osteoporosis for three years, the incidence of ONJ was very low at 0.017%.The incidence did not differ greatly in a study that was extended for three more years.

**(3) *Incidence according to the duration of treatment***

In a survey study of Kaiser Permanente members, which included 13,000 subjects, the incidence of ONJ related to oral bisphosphonate use was 0.1%. However, the incidence increased to 0.21% in patients who took the drug for more than four years.[13] Also, the median duration of bisphosphonate use was 4.4 years in patients who experienced ONJ, which is longer than the 3.5 years in patients who did not. Summarizing the results of several studies leads to a conclusion that ONJ occurs 100 times more frequently in cancer patients with bone metastasis than in osteoporosis patients.

#### 2) Incidence in cancer patients

The incidence of ONJ in cancer patients who were administered zoledronate is about 1%, which is 50 to 100 times higher than that seen in the control group (0% to 0.019%; 0 to 1.9 per 10,000 cancer patients).[14,15] Even in these patients the incidence of ONJ after zoledronate use is 0.6% for 1 year after, 0.9% for 2 years after, and 1.3% for 3 years after, showing an increase according to duration of use.[1,16,17]

## PATHOPHYSIOLOGY

There have been many pre-clinical and clinical studies on the pathophysiology of MRONJ, but the exact mechanism of why osteonecrosis occurs is under investigations. As shown in the definition of MRONJ, the exposure of bone plays an important role in determining the character of the disease.[18] In particular, there are many theories being presented on why this type of osteonecrosis only occurs on the jaw and not in other areas. Several review articles propose a relationship to excessive suppression of the jaw bone turnover, infection/inflammation, angiogenesis inhibition, soft tissue toxicity, the immune system, and accumulation of micro-fractures fractures.[19-28]

### 1. Suppression of bone turnover

Bisphosphonates inhibit the differentiation and promote apoptosis of osteoclasts, so that the resorption and formation of bone is decreased.[29] Based on the action mechanisms of these medications, it had been reported that bone turnover plays an important role in osteonecrosis.[29-31] The reason why osteonecrosis occurs in the jaw rather than in other long bones is explained by the strong suppression of the bone turnover in jaw bone after experimental bisphosphonate administration in preclinical study,[32] and more rapid cortical bone turnover in the human alveolar bone


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than in the long bones.[33] However, there is contradictory opinion based on the facts that bone turnover is not decreased in the ONJ lesion,[21] osteoclasts exist in the osteonecrotic areas, and that active bone resorption is occurring in these areas.[22,34,35]

### 2. Infection/inflammation

It is not clearly defined whether osteonecrosis occurs first and then the necrotic lesion becomes to be infected, or infected lesion becomes to undergo osteonecrosis. Since the active resorption does not occur in bisphosphonate-containing bone, the infected tissue is not readily removed completely and can easily progress to chronic osteomyelitis.[36-38] There are also experimental evidences which show that infection and bisphosphonate administration are necessary and serve as sufficient conditions for osteonecrosis.[39] Moreover, bisphosphonates are known to have an effect on the formation of a bacterial biofilm in the lesion.[21,36] However, it was difficult to find the specific infection focus in many of reported MRONJ cases.[40-43] Therefore, it is not clear whether the osteonecrosis develops after the progression of infection.

### 3. Angiogenesis inhibition

Bisphosphonates have an anti-angiogenic effect.[44-46] Osteonecrosis is regarded as a result of the deficiency in blood supply, therefore, it has been suggested that the angiogenic inhibition may explain pathophysiology of the osteonecrosis.[26,28] However, in animal studies, experimentally induced MRONJ-like lesions did not show the vascular insufficiency.[21,35,47] Moreover, it is difficult to explain why the osteonecrosis develops in circulation-rich upper jaw rather other long bones. Recently, there are several reports about osteonecrosis of the jaw which happened after administration of anti-angiogenic agents (sunitinib or bevacizumab) in cancer patients.[48-51] Additional clinical studies are needed to verify whether angiogenesis inhibition can directly increases the incidence of osteonecrosis.

### 4. Soft tissue toxicity

Although bisphosphonates primarily act on osteoclasts, they also have direct toxicity towards soft tissues such as oral epithelial cells. Bisphosphonates suppress the proliferation and transportation of oral keratinocytes, [26,52,53] which can increase the chances of latent bone exposure and subsequent infection. Thus, various types of tissue trauma, such as tooth extraction, may create an intraoral lesion and may lead to osteonecrosis.[22,54] However, after reaching the bloodstream, bisphosphonates are mostly excreted through the kidneys after a few hours, and the concentration of bisphosphonates in tissues other than the bone are reported to be quite low.[55]

### 5. Immune-related, or hair-line fracture-related theories

Bisphosphonates control the activity of various cells which involve in the immune response.[56,57] The risk of osteonecrosis after tooth extraction becomes significantly higher if steroids [17] or chemotherapeutic agents,[58,59] which may influence the innate/acquired immune system, are given during bisphosphonate administration.

Bone tissue is constantly undergoing the repetitive micro-fractures and healing process throughout the life, and such micro-trauma is slowly accumulated by age.[60] Micro-fractures caused by normal mastication are slowly accumulated due to the suppressive effect of bisphosphonates on osteoclasts or osteoblasts, resulting in latent osteonecrosis lesions.[61] Bacterial invasion of these lesions may cause progression to a deeper infection.[24,32] The results of various animal studies would support above-mentioned hypotheses. However, there are also many contradictory evidences that do not support such theories. Therefore, MRONJ is probably caused by multiple, combined factors that cannot be explained by a single pathophysiologic mechanism.

## RISK FACTORS

### 1. Systemic factors

Risk factors of MRONJ can be divided into local or systemic factors. Studies on systemic risk factors for MRONJ are mostly through retrospective analysis, so there are limitations on drawing a definite conclusion. Prospective studies are needed to report on the causality, and factors that have been suggested through studies are as listed below.

#### 1) Duration of bisphosphonate use

The increase of bisphosphonate use duration increases the risk of MRONJ. The reported incidence in the first one

or two years of use is 0%, but this increases after four years of use to about 0.21%. While the average duration of bisphosphonate use in the non-MRONJ group was 3.5 years, it was 4.4 years in the MRONJ group.[62] In Korean studies, MRONJ occurred 2 to 10 years after the use of bisphosphonates for the treatment of osteoporosis.[1,63,64]

#### 2) Use of steroids

The risk of MRONJ increases in patients on steroids.[65,66] The reason for this is thought to be due to decreased immune cells and delayed wound healing related to steroid use, which in turn exacerbates oral inflammation and increases the risk of MRONJ. However, the difference in incidence of MRONJ caused by the use of medications is mostly based on the results of retrospective studies, therefore, further prospective studies are needed.

#### 3) Old age

MRONJ shows an increasing trend in patients of old age. It has been reported that the prevalence increases in patients older than 65 years of age,[67] and a similar trend has been reported in local studies, with the highest prevalence seen in patients 75 to 79 years of age.[5]

#### 4) Diabetes

The risk of MRONJ is increased in diabetes patients.[68,69] This is thought to be due to decreased bone quality following ischemia of capillaries, decreased function of vascular endothelial cells, and increased apoptosis of osteoblasts and osteocytes caused by diabetes, in addition to decreased function of immune cells and increased inflammation seen in diabetes.

#### 5) Suppressed bone turnover markers

The relation between excessive suppression of C-terminal telopeptides of type I collagen (CTX), a bone resorption marker, and MRONJ incidence has been reported in several studies. However, a correlation between CTX level and severity of MRONJ has not been observed. There is still much controversy on whether a relationship exists between CTX levels and MRONJ incidence.[70-72] Ultimately, CTX decrease can be used as marker for the excessive use of bone resorption inhibitors, and although some studies have reported that there is a relation to MRONJ risk increase, there is still not enough evidence to conclude that the degree of CTX suppression has diagnostic value or is a risk factor of MRONJ.

#### 6) Genetic factors

There are reports that certain single nucleotide polymorphisms (SNPs) are related to the incidence of MRONJ. What has been elucidated so far is that most of the relevant SNPs are in genes related to bone turnover, collagen formation, or certain metabolic bone diseases, such as collagen type I alpha1 (COL1A1), receptor activator of nuclear factor-kappa B (RANK), matrix metallopeptidase 2 (MMP2), osteoprotegerin (OPG), and osteopontin (OPN).[73] As such, through reports on the significant relationship between certain SNPs and MRONJ incidence, the possibility of genetic susceptibility to MRONJ incidence is being suggested.

#### 7) Other systemic factors

Besides the factors outlined above, anemia,[68] hyperthyroidism,[58] dialysis,[17] etc. have been reported as systemic factors that increase the risk of MRONJ.

### 2. Local factors

There is limited information on the local factors of MRONJ incidence. However, MRONJ is reported to occur more frequently in the mandible rather than the maxilla, and the use of dentures can also increase the risk of incidence. Other reported local factors are listed below.

#### 1) Intraoral surgery that invades the alveolar bone, such as tooth extraction

#### 2) Local anatomical factors

Protruded bone surfaces are covered by relatively thin mucous membranes, so that continuous irritation by dentures, etc. can lead to exposure of the surface and contribute to the pathogenesis of MRONJ. Other anatomical landmarks such as a mandibular torus, the mylohyoid ridge, or a palatine torus can be vulnerable anatomic structures and act as local risk factors.

#### 3) Concomitant oral disease

In cases with other gingival diseases, dental or gingival abscesses, etc., MRONJ is known to occur more frequently.


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## MANAGEMENT

### 1. Prevention of MRONJ

A multidisciplinary approach is recommended for the management of MRONJ. When considering bisphosphonate treatment, there are cases which warrant a dental consult, and appropriate consultation not only decreases the incidence of MRONJ, but also has the advantage of securing the patient's oral health.[52,74-80] Compared to retrospective studies on patients who did not receive dental examination before bisphosphonate administration, there are numerous prospective studies that show a decrease in MRONJ when a dental examination is performed before treatment.[65,81-84] Education about the risk of MRONJ and dental consultation could be helpful to reduce the risk of MRONJ in patients taking bisphosphonates who are at high risk for the development of MRONJ.

① Though minimal, there is a risk of MRONJ occurrence in patients taking bone resorption inhibitors such as bisphosphonates.

② The importance of oral healthcare is emphasized to the patients for the prevention of MRONJ.

**Drug holiday**

Regarding the necessity of a drug holiday in patients scheduled for dental procedures that require bone recovery such as tooth extraction

#### 1) Patients taking oral bisphosphonates for the treatment of osteoporosis

In the 2011 revised guidelines of the American Dental Association (ADA) Council on Scientific Affairs, the recommendation is that for patients with a bisphosphonate treatment period of less than 2 years, invasive dental procedures be performed without a drug holiday,[77] while in the International ONJ Task Force guidelines, if the bisphosphonate treatment period is more than 4 years or if there are concomitant risk factors, a drug holiday is recommended until the bone is completely healed.[85] However, according to the 2011 report, the U.S. Food and Drug Administration (FDA)'s stance is that there is not enough evidence yet on the necessity of drug holidays to draw a conclusion. American Association of Oral and Maxillofacial Surgeons (AAOMS) recommends a drug holiday of 2 months based on a report [86] with evidence in bone physiology and pharmacodynamics, therefore, clinical validation is necessary. This committee conclusively recommends a drug holiday of 2-4 months.

#### 2) Patients taking intravenous bisphosphonates as anticancer treatment

The risk of MRONJ after dental treatment is greatly increased in cases of high dose intravenous bisphosphonate treatment compared to low dose oral treatment. However, although the necessity of a drug holiday is clear in cases of MRONJ, there is little evidence on whether a drug holiday is needed in advance for prevention, therefore, it is difficult to come to a definite conclusion.

### 2. Management strategies

#### 1) Patients scheduled for bisphosphonate administration for the treatment of osteoporosis

(1) Educate the patient on the fact that the risk of MRONJ is low for the time being, but becomes higher if treatment is maintained for more than 4 years.

(2) Although it is not mandatory, dental consult would be helpful to lower the risk of MRONJ by discovering conditions in which inflammation can easily occur in patients scheduled to receive bone resorption inhibitors such as bisphosphonate. Specific guidelines for dental specialists are as follows.[87]

① Motivation of the patient on maintaining oral health

② Oral healthcare education, such as dental care, fluorine coating, antibacterial oral rinse, etc. for patients

③ Evaluation of mobile teeth, gingival disease, root remnants, dental caries, periapical lesions, edentulous states, and denture stability

#### 2) Patients receiving bisphosphonates for the treatment of osteoporosis with no symptoms of MRONJ

Important factors to consider are the duration of bisphosphonate treatment and the presence of clinical risk factors. There is an increased risk of ONJ in patients who have received oral bisphosphonates for more than 4 years.[88] Although the risk is lower than that seen in cancer patients receiving high dose intravenous bisphosphonates, ONJ can also occur in patients receiving low dose oral bisphosphonates for osteoporosis.[88] Because these patients generally show milder symptoms compared to intravenous treated patients, and show a better response to treatment given according to stage,[62,89] elective dentoalveolar surgery is not prohibit-

ed. If the oral treatment period is over 4 years, or even if the treatment period is less than 4 years if there are concomitant risk factors such as steroid use,[51,65,90] the patient should be considered at high-risk for ONJ. If the patient's performance status allows it, drug holiday before elective dental surgery should also be considered.[66,86]

Because the value of bone turnover markers, which allow us to estimate the degree of bone formation and resorption, has not been proved yet,[70,71,91-93] it is not recommended as a tool for estimating risk factors, but further studies are needed.

**(1) *Patients with a duration of oral treatment less than 4 years and with no clinical risk factors***

Most dental treatment schedules, including oromaxillofacial surgery, do not need to be altered. If a dental implant placement is scheduled and bisphosphonate treatment is continued, despite the low possibility, a informed consent explaining the increased risk of MRONJ due to bisphosphonate treatment is recommended.[94] The consent form should include an explanation that even if there are no problems at the time of placement, the implant may fail over a long period of time, and that although the risk of ONJ is very low. For a more thorough consent form, additional supporting clinical studies are needed in the future. Discussion on dose adjustment, drug holiday, or switching to another osteoporosis drug can take place between the bisphosphonate prescribing physician and the dental specialist.

**(2) *Patients with a duration of oral treatment less than 4 years but with clinical risk factors such as concomitant use of steroids or angiogenesis inhibitors, diabetes, etc.***

Before dental treatment of a patient taking bisphosphonates, the bisphosphonate prescribing physician and the dental specialist, provided that the patient's systemic condition allows it, may order a drug holiday of more than 2 to 4 months, and after the dental treatment, readministration of bisphosphonates should be done after bone healing is complete. Because the results of clinical studies so far are limited, accumulation of long term prospective studies are needed in the future.

**(3) *Patients with a duration of oral treatment longer than 4 years regardless of clinical risk factors***

After consulting with the bisphosphonate prescribing physician, if the patient's condition allows it, a drug holiday of at least 2 to 4 months should be taken before dental treatment. Before dental treatment of a patient taking bisphosphonates, the bisphosphonate prescribing physician and the dental specialist, provided that the patient's systemic condition allows it, may order a drug holiday of more than 2 to 4 months, and after the dental treatment, readministration of bisphosphonates should be done after bone healing is complete. Further studies are needed on the long term effects of oral bisphosphonate treatment.

### 3) Patients scheduled for intravenous bisphosphonate administration for anticancer treatment

The goal of treatment is minimization of ONJ occurrence. The majority of patients taking bisphosphonates get ONJ after alveolar bone surgery,[65,67,95] therefore, bisphosphonate administration should be initiated after oral health conditions are optimized.[81,82] Drug administration and dental care should be dependent on consultation to the relevant specialists. Hemato-oncologists should care for patients scheduled for intravenous bisphosphonate treatment as they do for patients scheduled for radiation therapy. Dental care that may help in optimizing oral health is as follows.

① Extraction of teeth that are untreatable or have a bad prognosis and completion of all nonemergent dental treatment

√ Things to check before bisphosphonate readministration after dental treatment

Completion of bone healing of the area that was treated (re-epithelialization)

② Necessary factors to maintain functionally healthy teeth

Completion of appropriate preventive dental treatment

Control of dental caries

Conservative restorative treatment

③ Care of patients with dentures

Control of ill-fitting denture surfaces (especially the tongue surface) in order to minimize mucosal trauma

④ Patient education

Oral hygiene

Regular visits to the dentist

Immediate notice in case of symptoms such as pain, swelling, alveolar bone exposure, etc.


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#### 4) Patients receiving intravenous bisphosphonates for anticancer treatment with no symptoms of ONJ

The most important thing is to avoid situations in which alveolar bone surgery is needed, and in order to do so, oral hygiene and control of dental caries is needed. Untreatable dental crowns should be boldly eliminated, and endodontic treatment of the remaining root should be done. Although there is not much known about the risk of ONJ due to dental implantation in patients receiving intravenous bisphosphonate treatment, it is better not to perform implant treatment in these patients.

#### 5) Patients with symptoms of MRONJ

The efficacy of surgical [89,96-100] and conservative [101-105] treatment has been reported for the various stages of ONJ. The treatment goal for patients who already have progressive ONJ is the alleviation of pain due to necrosis, infection control of the necrotic tissue, and prevention of osteonecrosis progression. MRONJ related to the administration of oral bisphosphonates for osteoporosis patients is generally considered to have weaker, and to be more responsive symptoms to the treatment than those derived from oncologic indication of bisphosphonates.[90] Surgical treatment is generally thought to be quite successful although further progress of necrosis might occur. In advanced stage 3 cases, surgical treatment should be carefully considered. In cases where a sequestrum is formed, distinctly the necrotic tissue is easily separated from the surrounding healthy tissue.[101,103] Regardless of the stage, osteonecrotic area that may irritate the soft tissue and loosely attached necrotic bone fragments should be removed or grinded off so that soft tissue healing is normalized.[106] If symptomatic teeth (teeth that are the cause of pain or that are extremely loose) are attached to the necrotic bone, extraction should be considered, as it is believed not to exacerbate the necrosis. A randomized controlled trial of hyperbaric oxygen (HBO) showed a possibility as an adjunct therapy,[107] but in the trial, statistical verification was not possible with regard to the major endpoint of the study of "complete healing of soft tissue", due to a small sample size. Therefore, HBO therapy may not be recognized as a sole treatment method for MRONJ and further study results should be followed. There are numerous case studies being reported on adjunct methods such as platelet-rich plasma (PRP) treatment,[108,109] laser treatment,[110-112] parathyroid hormone (PTH) treatment,[113,114] bone morphogenetic protein (BMP) treatment,[108,115] etc. but none are fully proven yet.

#### 6) Staging and treatment strategy for patients with MRONJ symptoms

After Stage 0 was newly added to the 2009 AAOMS Staging Guidelines, given that close to 50% of all cases in this stage progress to a higher stage,[34,116] the addition of Stage 0 appears to be valid. The addition of the 'At risk stage', considered by this committee, is meaningful in that it aims to include all patients on bisphosphonates in the ONJ care group for the purpose of prevention.

**(1) *At risk category***

This category includes patients that are taking bisphosphonates or who, although have no symptoms of osteonecrosis, are exposed to bisphosphonates or have a history of bisphosphonate exposure. Education on the risk of ONJ occurrence and oral hygiene should be emphasized.

**(2) *Stage 0***

With no clinical symptoms of osteonecrosis, but with nonspecific or clinical symptoms such as toothache, bone pain, dysesthesia, etc. and radiographic signs such as maxillary sinus mucosal thickening, etc. occurring at the same time.

√ Symptoms
- Toothache that is judged to be not of dental origin, such as dental caries or gingivitis
- Bone pain in the form of a deep, dull ache, that begins in the mandibular body and moves to the temporomandibular joint
- Maxillary sinus pain that appears to be associated with maxillary sinus mucosal thickening or inflammation
- Dysesthesia

√ Clinical symptoms
- Tooth mobility not due to gingivitis
- Gingival fistula unrelated to pulp necrosis

√ Radiographic signs
- Alveolar bone loss without chronic gingivitis
- Change in trabecular form-sclerosis of spongy bone, tooth extraction and poor bone remodeling
- localized bone sclerosis that reaches the alveolar bone

or the basal bone
- Hypertrophy of the lamina dura and narrowing of the periodontal ligament space

√ Treatment strategy

Conservative treatment such as pain control is needed, and localized causes such as dental caries or gingivitis is managed conservatively. Systemic treatment, such as drugs for chronic pain control or antibiotics, is needed. The disease may progress in up to half of all patients who only show radiographic signs, therefore, close monitoring is needed.

**(3) *Stage 1***

√ Symptoms

Osteonecrosis with no signs of infection or fistula that reaches the bone upon probing is seen. Radiographs may show signs that are seen in Stage 0.

√ Treatment strategy

Antibacterial oral rinse may help and immediate surgery is not needed. Patient education and re-evaluation is needed on whether bisphosphonates are still necessary.

**(4) *Stage 2***

√ Symptoms

Osteonecrosis with signs of infection (pain and erythema of the area of osteonecrosis) and the presence of a fistula is characteristic, and symptoms related to infection are typically present. Radiographs may show signs that are seen in Stage 0.

√ Treatment strategy

Antibacterial oral rinse and antibiotics must be prescribed. Although the infection is not the main cause of ONJ, bacterial accumulation in the necrotic area is commonly observed and is usually controlled by penicillin. The formation of a bacterial membrane in the mouth is common, and may also occur in the necrotic area. This membrane has been reported to interfere with the efficacy of systemic antibiotics.[54-56] Besides this, pain control with analgesics, and removal of bone fragments that irritate the soft tissue is also possible.

**(5) *Stage 3***

√ Symptoms

Osteonecrosis with signs of infection (pain and erythema of the area of osteonecrosis) and the presence of a fistula occurs with the following symptoms.

A. The extension of osteonecrosis beyond the alveolar bone (mandibular inferior border, maxillary sinus, etc.)
B. Pathological fractures
C. Orocutaneous fistula
D. Oronasal- & oroantral fistula
E. Osteolysis extending to the mandibular inferior border or the base of the maxillary sinus upon the panoramic radiograph

√ Treatment strategy

Pain control, antibacterial oral rinse, and infection control through antibiotic treatment is needed, and for the long term alleviation of infection or pain, surgical debridement or resection is necessary. If a sequestrum is distinctly formed so that the tissue is easily separated from the surrounding healthy tissue, or if there is a tooth in the middle of the sequestrum, the necrotic bone is not exacerbated by extraction, therefore, any mobile bone fragments or teeth should be removed. Because there may be cancer metastasis, the removed bone fragments should be examined.[117] Immediate reconstruction after surgical resection has been reported,[118-120] but clinicians must make a decision after thoroughly considering the patient's condition.

## MEDICAL MANAGEMENT OF PATIENTS WITH MRONJ

### 1. Drug holidays and drug replacements

Whether related to a malignancy or to osteoporosis, once ONJ occurs, it is inevitable that bisphosphonates are discontinued or the patient is entered into a drug holiday with no scheduled termination. Because one of the reasons for ONJ occurrence is the excessive suppression of bone reformation by long term bisphosphonate use, by terminating bisphosphonates one must expect that the bone reformation process recovers. In a study by Marx et al.[89] the level of serum CTX, a bone resorption marker, of all ONJ patients was less than 100 pg/mL, and after a drug holiday of 3 months, the levels increased to more than 150 pg/mL in all patients, showing that a drug holiday may be beneficial to the recovery of the bone formation process. Meanwhile, with the concern of recent severe adverse events such as ONJ and atypical fractures, there have been many recommendations by experts on having a drug holiday after 3 to 5 years of bisphosphonate treatment before such adverse events occur.[121] However, even in such cases, a


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drug holiday is not recommended in all situations, and for cases that have a high risk of fracture, bisphosphonate treatment is maintained, as is for ONJ cases that have severe pain due to bone metastasis in cancer patients, or that have severe hypercalcemia, or in osteoporosis patients who have a high risk of fracture. For pain related to malignancies or for hypercalcemia, calcitonin can be given, and for osteoporosis patients, selective estrogen receptor modulators (SERMs) can be considered. However, the biggest problem is that for the drugs used as replacements during a bisphosphonate holiday, there are no large scale studies proving their efficacy, durability, or influence on ONJ. In cases related to malignancies, there have been some attempts to carefully readminister bisphosphonate during or after recovery of ONJ.

## 2. Recombinant human PTH 1-34 (teriparatide) treatment

Teriparatide is the only bone formation accelerator among all drugs used for the treatment of osteoporosis in Korea. It stimulates osteoblasts and osteoclasts while inhibiting the apoptosis of osteoblasts, showing an increase in bone density and excellent efficacy in preventing fractures.[122,123] The bone remodeling stimulatory effect of teriparatide has been shown to be effective even in patients with suppressed bone remodeling processes due to the use of bone resorption inhibitors such as bisphosphonates.[124-126] Recently, there have been many reports that teriparatide may play positive roles in the treatment of ONJ. In 2010 Cheung and Seeman [127] treated an ONJ patient with teriparatide for 8 weeks, upon which the patient's symptoms improved and the ONJ area healed completely, leading the authors to report that teriparatide is effective as a treatment for ONJ. Also, another study was reported in that similar period in which teriparatide injection treatment was given for 6 weeks to patients with gingivitis who had pathological findings similar to ONJ, and the patients who received treatment showed improvement of markers related to gingivitis recovery compared to those who did not receive treatment.[114] Afterwards, through several case reports, it has been reported that using short term teriparatide in ONJ patients showed large improvements in the disease.[128,129] Such effects of teriparatide on ONJ are expected to be due to the stimulation of bone remodeling through stimulation of osteoblasts and osteoclasts, and when used in ONJ patients, a significant recovery of suppressed bone turnover markers including bone resorption markers and bone formation markers could be seen.[63] Recently, ONJ patients untreatable by conservative treatment methods were given subcutaneous teriparatide 20 μg daily for 6 months, and were compared with patients unable to receive teriparatide for other reasons on ONJ treatment results after 6 months.[130] Regarding the changes in bone markers, as expected, osteocalcin, the bone formation marker, began to increase significantly 1 month into treatment, and CTX, bone resorption marker, followed after 3 months, showing that teriparatide treatment is effective in reactivating the bone remodeling process that was suppressed due to bisphosphonate treatment.[130] Moreover, regarding the final 6-month treatment results in ONJ status, while 40% of the patients who did not receive teriparatide did not show an improvement in disease, and only 60% showed partial improvement of the ONJ lesion, 62.5% of the patients who received teriparatide treatment showed complete resolution of the disease. There results show us that teriparatide is also effective for the treatment of severe ONJ patients who do not respond to conservative treatment.[130] Through such various clinical studies, there is increasing evidence on the positive role of teriparatide in the treatment of ONJ patients, and this effect is seen not only due to the stimulatory effect on bone remodeling of teriparatide, but also due to its stimulation of angiogenesis.[131] Furthermore, when taking into account the fact that ONJ patients are also osteoporosis patients, the use of teriparatide is also beneficial when seen from the perspective of osteoporosis treatment.

## 3. Vitamin D and calcium

Appropriate vitamin D and calcium intake is the basic fundamental of osteoporosis prevention and treatment. Therefore, although ONJ patients may discontinue bisphosphonate, appropriate vitamin D and calcium supplementation should be continued. Certain recent studies have shown that the concentration of serum vitamin D is positively correlated to the amelioration of gingivitis or the degree of recovery after gingival surgery, and the maintenance of an appropriate concentration of vitamin D is thought to be important for the recovery of ONJ.[132,133] Even when using the previously introduced teriparatide for ONJ treatment, an appropriate vitamin D level has been reported to

be a factor that can increase the effect of the drug.[130] Therefore, ONJ patients must continue supplementation of vitamin D and calcium for the amelioration of gingivitis or the prevention of osteoporosis.

## CONCLUSION

Bisphosphonates are effective drugs for treating osteoporosis and preventing fractures. Although the incidence rate is very low, MRONJ can occur when bisphosphonates are administered for long time period. Discontinuation of bisphosphonate treatment is recommended if MRONJ occurs. In cases of bisphosphonate discontinuation, drug replacements may be considered according to individual patient conditions such as malignant bone metastasis or osteoporosis. However, the efficacy or relation to ONJ recovery of such replacements has not been proven through large-scale clinical studies; therefore, a careful approach is necessary. Basic conservative treatment to surgery is possible for the treatment of ONJ. Despite such dental treatments, if ONJ has progressed, teriparatide, a bone formation accelerator, can help with the recovery of ONJ. Vitamin D concentration is known to be related to gingivitis or gum recovery; therefore, vitamin D and calcium supplementation can prevent not only the exacerbation of osteoporosis, but should be continued in that it can also help in the treatment of ONJ.

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