

原文題目(出處)：	Osteonecrosis of the jaws secondary to bisphosphonate therapy: a case series (The Journal of Contemporary Dental Practice Volume 9 Number 1 January 1, 2008)
原文作者姓名：	Kumar SKS, Meru MC, Sedghizadeh PP.
通訊作者學校：	Clinical Dentistry, University of Southern California
報告者姓名(組別)：	Intern A組 呂承威 康雅婷
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內文：

Introduction of bisphosphonates ( BPs )

- Treatment of osteoporosis, cancer metastases to bone, hypercalcemia of malignancy, multiple myeloma
- Treatment of refractory bone pain
- Reduction of pathologic vertebral fractures and pain
- Prevention and treatment of corticosteroid-induced bone loss
- Direct anti-cancer effects
- Attenuate or prevent morbidity associated with osteoporosis-related fractures
- High affinity for bone
- Anti-osteoclastic & anti-angiogenic properties  
→ affecting osseous remodeling

Side effects of bisphosphonates

- GI tract intolerability
- Symptomatic hypocalcemia
- Bone stress fractures
- Influenza-like illness
- Myalgia
- Deterioration of renal function
- Renal failure
- Acute tubular necrosis
- Esophageal erosion & ulceration
- Anti-angiogenic effects

Their prevalence is low & little toxicity in animal studies

- Osteonecrosis affecting the jaw bones  
→ nitrogen-containing > non-nitrogen  
→ intravenous therapy > oral therapy

Case report ( A series )

Table 2. Clinico-pathologic parameters in patients with ONJ secondary to BP therapy.

Patient	Age/ Sex	Ethnicity	Medical condition for bisphosphonate intake	Other medical & co-morbid conditions	BP administered	Duration	Predisposing Dental Procedure	Location of osteonecrosis	Treatment
#1	75/F	Asian-American	Breast cancer	Chemotherapy, radiotherapy, hypertension	Zoledronic acid 4mg IV once/ month	48 months	Tooth Extraction & Denture Trauma	Right & left mandible	Antibiotics, local debridement, spontaneous sequestration, daily chlorhexidine mouth rinsing
#2	67/M	Hispanic-American	Prostate cancer	Steroid therapy for chronic adrenal insufficiency, chemotherapy, anemia	Pamidronate 90mg IV once/ month	36 months	Tooth Extraction	Left maxilla	Antibiotics, local debridement, spontaneous sequestration, daily chlorhexidine mouth rinsing
#3	71/M	African-American	Multiple myeloma	Hypertension, hyperthyroidism, schizophrenia, depression	Zoledronic acid 4mg IV once/ month	24 months	Denture Trauma	Entire maxilla & mandible	Antibiotics, local debridement, sequestrectomies, daily chlorhexidine mouth rinsing
#4	68/M	African-American	Multiple myeloma	Type II diabetes, hypertension, dyslipidemia, osteoarthritis	Zoledronic acid 4mg IV once/ month	8 months	Tooth Extraction	Right mandible	Antibiotics, local debridement, daily chlorhexidine mouth rinsing, soft stent to cover bone exposure
#5	73/F	Asian-American	Osteoporosis	Hypertension, hypercholesterolemia, osteoarthritis, gastroesophageal reflux disease	Alendronate 70mg PO once/ week	36 months	Denture Trauma	Left mandible	Daily chlorhexidine mouth rinsing
#6	80/F	Asian-American	Osteoporosis	Type II diabetes, osteoarthritis, stroke, heart stent	Alendronate 70mg PO once/ week	120 months	Denture Trauma	Left maxilla	Discontinuation of alendronate, Antibiotics, local debridement, daily chlorhexidine mouth rinsing
#7	74/F	Asian-American	Osteoporosis	Peptic ulcer	Alendronate 70mg PO once/ week	60 months	Denture Trauma	Right mandible	Antibiotics, local debridement, daily chlorhexidine mouth rinsing
#8	75/F	Hispanic-American	Osteoporosis	Hypercholesterolemia, hypothyroidism	Alendronate 70mg PO once/ week	36 months	Denture Trauma	Right & left mandible	Antibiotics, daily chlorhexidine mouth rinsing
#9	79/F	Asian-American	Osteoporosis	Type II Diabetes, Hypertension, hypercholesterolemia	Alendronate 70mg PO once/ week	60 months	Tooth Extraction	Right mandible	Discontinuation of alendronate, Antibiotics, local debridement, daily chlorhexidine mouth rinsing

Table 2. Clinico-pathologic parameters in patients with ONJ secondary to BP therapy.

Patient	Age/ Sex	Ethnicity	Medical condition for bisphosphonate intake	Other medical & co-morbid conditions	BP administered	Duration	Predisposing Dental Procedure	Location of osteonecrosis	Treatment
#10	63/F	Hispanic-American	Osteoporosis	Hypertension, chemotherapy and steroid therapy for rheumatoid arthritis	Alendronate 70mg PO once/ week	36 months	Denture Trauma	Right maxilla	Discontinuation of alendronate Antibiotics, sequestrectomy, local debridement, daily chlorhexidine mouth rinsing
#11	74/F	Asian-American	Osteoporosis	Hypertension, hypercholesterolemia	Alendronate 70mg PO once/ week	12 months	Tooth Extraction	Right mandible	Discontinuation of alendronate Antibiotics, sequestrectomy, local debridement, daily chlorhexidine mouth rinsing
#12	76/F	Asian-American	Osteoporosis	Cancers (ovary, uterus, colon, liver), chemotherapy, hypertension, asthma	Alendronate 70mg PO once/ week	120 months	Tooth Extraction	Left mandible	Discontinuation of alendronate, partial sequestrectomy, local debridement, daily chlorhexidine mouth rinsing
#13	65/F	Asian-American	Osteoporosis	Hypertension, hypercholesterolemia	Alendronate 70mg PO once/ week	12 months	Tooth Extraction	Left mandible	Local debridement, daily chlorhexidine mouth rinsing

- Type of BP used
- Medical conditional being treated
- Duration of use
- Other medical & co-morbid conditions
- Location of osteonecrosis
- Inciting factor such as previous dental extractions or dental trauma to the site
  
- Radiographs : panoramic X-rays for all patients  
cone-beam CT for selected patients
- Ill-defined lytic change with bony sequestrum & no signs of malignancy

Four of the cases are of the particular interest  
Patient #3 :

#3	71/M	African-American	Multiple myeloma	Hypertension, hyperthyroidism, schizophrenia, depression	Zoledronic acid 4mg IV once/month	24 months	Denture Trauma	Entire maxilla & mandible	Antibiotics, local debridement, sequestrectomies, daily chlorhexidine mouth rinsing
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- Wear complete maxillary & partial mandibular denture for almost a year without remove
- Severe osteonecrosis of entire maxilla & most of the mandible



Figure 1. Extensive ONJ of the upper jaw in patient #3 showing nothing but maxillary skeleton coated with white plaque-like debris in addition to a reactive granulation tissue-like response involving the palate.



Figure 2. A three-dimensional reconstruction of the cone-beam CT scan demonstrates the extensive bony destruction of the mandible and maxilla. The maxillary involvement extends to the maxillary sinus while the mandibular involvement extends inferiorly to the level of the mental foramen.

Case 2 :

- The second case is patient #6, who is an 80-year-old Asian-American female
- Osteoporosis and was taking alendronate orally once weekly for nearly ten years
- ONJ in the left maxillary quadrant with an oro-antral fistula and active, draining purulence.
- Had being managed with systemic antibiotic therapy, chlorhexidine mouth rinses several times daily, and conservative debridement of bony sequestra as needed.
- The patient had discontinued alendronate and seven months after cessation of alendronate, bone destruction and ONJ continues.

Case 3 :

- The third case is patient #10, who although had been on oral alendronate for only 36 months was wearing her partial denture almost 24 hours/day and only removing it while brushing her remaining teeth twice daily.
- She presented with a large exposed painful sequestration in the right maxillary quadrant without oro-antral communication.
- This patient underwent conservative sequestrectomy and is being managed with systemic antibiotic therapy and chlorhexidine mouth rinses several times daily.
- This case clearly shows the critical role of inciting trauma despite the relatively low duration of BP intake.

Case 4 :

- The fourth case is patient #5 who is an Asian-American female referred to the clinic for left temporomandibular joint ‘crepitation’ and occasional pain on function.
- Her medication included alendronate PO once weekly for 36 months, and the site of ONJ intra-orally in the mandible was an incidental finding.
- The patient was partially edentulous with most of the posterior teeth missing and was wearing maxillary and mandibular partial dentures. On intra-oral examination, a mucosal ulcer measuring approximately 1 mm in diameter was

noted at the left mandibular alveolar ridge with no evidence of inflammation or infection

- On probing, the periodontal probe dropped ≥10 mm into the mandibular bone at the ulcer site. The patient reported no symptoms and denied having noticed any mucosal breakdown at the partially edentulous left mandibular ridge. No clinical expansion, paresthesia, or dysesthesia was noted.
- The patient was informed about the nature of her condition and is being managed with chlorhexidine mouth rinses several times daily and shows no signs of disease progression.

#### Conservative treatment

- Chlorhexidine rinses
- Oral antibiotics
- Gentle debridement
- Warm saline irrigation
- Soft acrylic stents were fabricated (when exposed or sharp bone would cause trauma to adjacent tissue)

#### Discussion

- Pathogenesis
- Diagnostic criteria
- Reported cases
- Significant
- No evidence-based therapeutic protocols exist
- Research into ONJ is needed at both the basic science and clinical level.
  
- ONJ secondary to BPs  
(clinically similar in appearance to radiation-induced ONJ or osteomyelitis of the jaws)
  - ✓ Oral mucosal ulcerations with bony sequestrum
  - ✓ Asymptomatic and painless
  - ✓ Persisted lesions
  - ✓ Do not respond well to conventional treatment modalities
  - ✓ Delayed or lack of tissue healing ∅ bony exposure and dehiscence
  - ✓ ONJ cannot be diagnosed until there is a frank clinical lesion be it necrotic bone exposure or secondary infection, swelling, and drainage.
  - ✓ Early ONJ without any clinical evidence does not show appreciable bony changes in a routine dental radiograph
- Ruggiero et al. has proposed a clinical staging and recommended therapy for each stage of ONJ.
  - ✓ ONJ secondary to BP therapy: long half-life of BPs in bone
    - time- and dose-dependent phenomenon
    - obtain a complete history for every patient who takes BP's
- ONJ secondary to alendronate
  - ✓ The risk of ONJ secondary to alendronate is of concern because several million women take this medication for prevention of post menopausal osteoporosis;
- More than half of all cases (60%) of ONJ have been reported to occur after dentoalveolar surgery (such as tooth extraction) to treat infections, and the remaining 40% were related to infection, denture trauma, or other physical

- trauma.
- Nitrogen-containing BPs (located on one of the R groups)
  - Non-nitrogen-containing BPs
    - ✓ Nitrogen-containing BPs inhibit critical enzymes of the mevalonate pathway, particularly farnesyl diphosphate synthase.
    - ✓ Nitrogen-containing BPs have been implicated in ONJ more than the non-nitrogen containing ones.
    - ✓ BPs suppress osteoclastic bone resorption, and oversuppression of osteoclasts
    - ✓ Blocking the activity of mature osteoclasts,
    - ✓ The induction of osteoclast apoptosis.
    - ✓ BPs also inhibit the formation and activation of osteoclasts by impairing the distribution of osteopontin, B3 integrin, Rac1, and Cdc42
    - ✓ The anti-resorptive potency of each BP varies, and zoledronic acid, which has the highest anti-resorptive potency ( $\geq 10,000$ ), has been implicated in more than 90% of ONJ cases.
    - ✓ Avascularity and antiangiogenic properties of BPs are also thought to be involved in the pathogenesis of ONJ.
  - Hypotheses :
    - ✓ The properties of the bones in the jaw are different than elsewhere in the body.
    - ✓ The jaws have a greater blood supply and a faster bone turnover rate
  - When combined with chronic invasive dental diseases and their treatment, these factors could provide the necessary circumstances for ischemic bone necrosis that could become secondarily infected, particularly when exposed to the oral cavity as sequestra
    - ✓ Many of Microbial flora in the oral cavity are involved in numerous dental/periodontal disease processes as well as with the induction of osteoclastogenesis.
    - ✓ Microbial flora in the oral cavity can come into direct contact with the bone due to the thin, easily traumatized epithelium, which does not usually occur elsewhere in the body.
  - Treatment
    - ✓ (1) Patients who will soon start BPs therapy : optimizing dental health is the primary goal
    - ✓ (2) Patients receiving BPs with no evidence of ONJ : maintain meticulous oral hygiene.
    - ✓ (3) Patients with established ONJ : depends on the clinical stage of their condition.
      - ◆ (3)-1. For patients with exposed, asymptomatic necrotic bone, daily antimicrobial rinses with 0.12% chlorhexidine (non-alcoholic) and regular clinical follow-up as dictated by the disease is recommended.
      - ◆ (3)-2. Those with exposed, necrotic bone associated with pain and infection, antibiotic therapies based on culture, analgesics, as well as daily antimicrobial rinses are recommended. (Penicillin VK, Levofloxacin, Amoxicillin and clavulanate, Clindamycin, Azithromycin, Doxycycline, Erythromycin ethylsuccinate Metronidazole )

- ◆ (3)-3. For patients with exposed, necrotic bone and in patients with pain, infection, and pathologic fracture, extraoral fistula, or osteolysis extending to the inferior border, surgical debridement of necrotic bone, antimicrobial therapy (PO or IV), analgesics, as well as daily antimicrobial rinses is recommended.
- Although there is no definitive cure for ONJ and most treatment is palliative, treating patients' dental and periodontal disease prior to initiation of BP therapy and treating symptoms to control or prevent the spread of ONJ and secondary infection is important.
- Once the diagnosis of ONJ has been made, there has been support for both continuing BP treatment and discontinuation of the drug for a period of time while managing the ONJ.

Conclusion

- BPs possess significant therapeutic benefits, and their use will continue to grow and eventually ONJ complications can be expected to rise until optimal dosing and duration of treatment are determined.
- Treatment of dental and periodontal infections and maintenance of good oral hygiene is critical before starting BP therapy in order to help prevent this significant complication of ONJ.

題號	題目
1	ONJ和ORN的相似處? (A) Oral mucosal ulcerations with bony sequestrum (B) Asymptomatic and painless (C) Persisted lesions (D) 以上皆是
答案(D)	出處：
題號	題目
2	下列何者治療方式不是conservative treatment? (A) ORN (B) ONJ (C) Osteomyelitis (D) Idiopathic osteosclerosis
答案(C)	出處：