原文題目(出處)：	Alternative Indications for Bisphosphonate Therapy. J Oral Maxillofac Surg 2009;67(Suppl 1):27-34.
原文作者姓名：	Landesberg R, Eisig S, Fennoy I, Siris E
通訊作者學校：	Columbia University College of Dental Medicine, New York, NY
報告者姓名(組別)：	黃于芳 Intern E組
報告日期：	99/02/08

內文：

Introduction

- BPs are pharmacological agents that inhibit osteoclastic bone resorption, are used in the treatment of
  - osteoporosis (postmenopausal and steroid-induced)
  - hypercalcemia of malignancy
  - Paget's disease of bone
  - multiple myeloma
  - metastatic bone disease in breast, prostate, lung, and other cancers
- Numerous other conditions where a decrease in bone remodeling by bisphosphonates might aid in disease management:
  1. giant cell lesions of the jaw
  2. giant cell tumors of the appendicular skeleton
  3. pediatric osteogenesis imperfecta
  4. fibrous dysplasia
  5. Gaucher's disease
  6. osteomyelitis

Giant Cell Lesions of the Jaws:

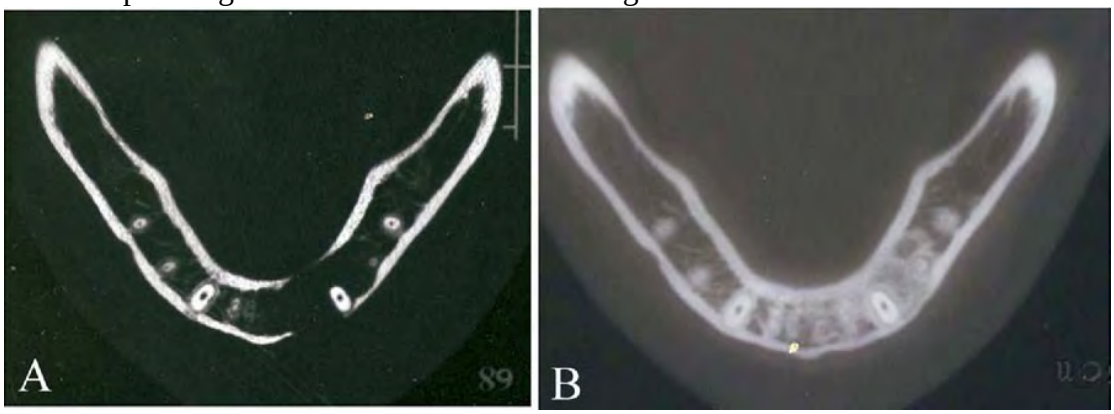
- Clinical features:
  - ✓ Age predilection:10~30 y/o
  - ✓ Site predilection: Maxilla and mandible
  - ✓ Symptom and sign: destructive, and may cause significant expansion and/or destruction of the cortical plates, resulting in marked facial deformities
- Histopathologic features:
  multinucleated giant cells in a hyperemic fibrous stroma
  (D.D.: cherubism / brown tumors of hyperparathyroidism)
- Treatment and prognosis:
  - ✓ Aggressive manner, recurrence rate of 11% to 50%
  - ✓ surgical extirpation is often difficult, especially when the lesion is contiguous with vital neural and/or vascular anatomy
  - ✓ medical therapies:
    - ♦ Intralesional injection of steroids (numerous painful injections)
      (*Pogrel*~ only about 50% of cases respond to steroid injections)
    - ♦ Subcutaneous calcitonin injections
    - ♦ Adjuvant intravenous α-interferon therapy in conjunction with surgical enucleation shows promise for the treatment of aggressive GCLs
- The authors have had varying experience using bisphosphonates (BPs) as a primary or adjunctive therapy in the treatment of GCLs of the jaws

Case Reports

PATIENT 1

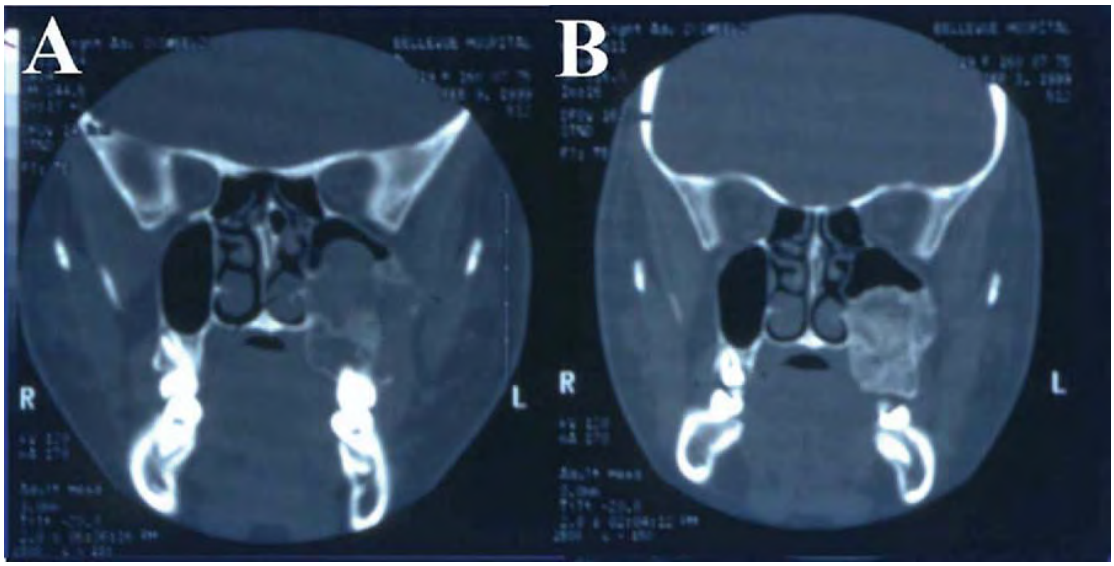
- ✧ General data: 17-year-old male

- ✧ C.C.: loosening of his teeth and pain in the left anterior mandible
- ✧ Panoramic radiograph: A radiolucent lesion
- ✧ CT scan (mandible) showed destruction of the buccal and lingual cortices by the lesion with osteolysis of the trabecular bone
- ✧ Laboratory data: normal serum calcium, parathyroid hormone, and alkaline phosphatase
- ◆ Initial treatment(˙.˙the difficulty of surgical extirpation&the need to remove the involved teeth): a single infusion of 4 mg of zoledronic acid
- ◆ Result: The lesion regressed, and a 6-month postinfusion CT showed nearly complete regeneration of the buccal and lingual cortices and sclerotic bone fill



PATIENT 2

- ✧ a 22-year-old Caucasian female with a GCL of the left maxilla
- ✧ Asymptomatic ,and was discovered on a routine panoramic radiograph
- ✧ Treatment: 2 intravenous infusions of 90 mg pamidronate at 6 month intervals
- ◆ Result: 30% reduction in the lesion size with considerable consolidation of the bone trabeculation



PATIENT 3

- ✧ A 56-year-old male with a large GCL in the anterior mandible
- ✧ Treatment: 3 doses of 4 mg zoledronic acid at yearly intervals
- ◆ Result: stabilization but no regression of the lesion.
  (The patient subsequently underwent successful surgical treatment, so it is not known if higher doses and/or frequency of drug administration would have shown a more favorable result)

BP Treatment of Giant Cell Tumors of Bone(GCTB)

- Clinical features:
  - ✓ Site predilection: meta-epiphyseal region of the distal femur or proximal tibia but is also reported in the vertebral, pelvic, and sacral areas
- Radiographic appearance: osteolytic bone destruction
- Benign lesions that rarely metastasize but may be locally aggressive with invasion of the surrounding soft tissues
- Treatment and prognosis:
  - ✓ local curettage and bone grafting
  - ✓ adjunctive therapies are often used including packing of bone cement (polymethyl methacrylate [PMMA]), cryotherapy, highspeed burring, cytotoxic chemical lavage (hydrogen peroxide, phenol, alcohol, methotrexate), and in extensive cases, wide excision
  - ✓ local recurrence rate :10% ~ 50%, often resulting in repeated surgical procedures.

◆ Result:

A significant decrease in local recurrence in the BP treated group (30% vs 4.2%) for all tumor stages ,and a decrease in recurrence rate of stage III tumors from 46% to 9%

Osteogenesis Imperfecta and BP Therapy:

- Osteogenesis imperfecta (OI) is a genetically inherited disorder characterized by fragile bones and decreased bone mass
- Patients may also exhibit short stature, dental abnormalities, bone deformities,and hearing loss
- 4 distinct groups19 (types I, II, III,and IV), which are due to mutations in the COLAα1& COLAα2 genes, usually inherited on an autosomal dominant basis
- Recently, 3 new clinical types(types V, VI, and VII) have been identified, categorized by variations in clinical presentation, autosomal recessive inheritance, and not associated with COLA gene mutations
- Treatment: surgery, rehabilitation therapy, and more recently, BPs
- *Glorieux*~ BPs are effective agents to reduce fractures and improve clinical outcomes in Children with severe OI.
- BPs : a) Antiresorptive activities mediated through osteoclasts
  b) Improve survival of osteocytes and osteoblasts.
- IV pamidronate therapy has become the standard of care for children with moderate to severe OI.
- Oral alendronate has also been used as a potential alternative to I V pamidronate.

Fibrous Dysplasia:

- Clinical features:
  - ✓ Age predilection: ＜30 y/o
  - ✓ Site predilection: the long bones, ribs, and craniofacial skeleton
- Characterization: replacement of medullary bone with abnormal fibrous tissue, which may result in decreased bone integrity with subsequent fracture and/or significant skeletal deformities
- “Jaws” : painless with a typical presentation of a slowly progressive deformity
- “appendicular skeleton” : pain and pathological fractures.
- may present in a single bone (monostotic) or involve several bones (polyostotic)
- McCune-Albright syndrome: polyostotic FD + melanotic pigmentations (Café-au-lait macules) + endocrine abnormalities (precocious puberty)
- A mutation in the stimulatory Gs alpha subunit of G protein causes an increase in cAMP and interleukin-6, resulting in excessive osteoclastic resorption and

abnormal osteoblastic differentiation

- BP therapy: decrease in bone pain and improvement in the radiographic appearance of the lesions

BP Treatment for Gaucher's Disease:

- Autosomal recessive lysosomal storage disorder
- caused by a deficiency of the enzyme β-glucocerebrosidase, resulting in the accumulation of glucocerebroside in monocytes and macrophages
- 3 clinical forms(characterized by the presence and severity of neurological symptoms)

  Type I: the most common form , without neuropathic symptomatology
  Type II: the most severe neurological involvement
  Type III is associated with subacute neurological pathology
- Severe bone pain or "bone crises," impaired mobility, osteopenia, avascular necrosis, osteosclerosis, or pathological fractures
- In the only available double-blind, placebo-controlled trial Wenstrup et al78 followed 34 adults(18-50 years old) with type I Gaucher's disease receiving enzyme replacement therapy.
  - Patients were treated with either 40 mg of alendronate or placebo daily for a period of 24 months.
  - Bone mineral density (BMD) absorptiometry, plain film radiographs of focal lesions, and serum bone turnover markers were monitored at 6-month intervals.
  - BP treatment resulted in a significant improvement in BMD after 18 months; however, there was no improvement in focal lesions.

BP Therapy for Osteomyelitis

- Chronic recurrent multifocal osteomyelitis (CRMO)
  - a rare condition that most commonly occurs in children and young adults
  - characterized by a chronic, sterile inflammation that usually involves the metaphyses of the long bones(~Giedion et al,1972)
  - The chest wall, pelvis,spine, and rarely the mandible may also be involved
- SAPHO syndrome(Synovitis, Acne, Pustulosis, Hyperostosis, Osteitis)
  - osteoarticular inflammation& neutrophilic pseudoabsess skin abnormalities
- CRMO is now considered a manifestation of the SAPHO syndrome
- diffuse sclerosing osteomyelitis (DSO) of the mandible has many clinical, radiographic, and histological similarities to CRMO and SAPHO
- (CRMO , SAPHO syndrome , DSO)all have an unknown etiology, recurrent pain, and are difficult to treat
- ✪ BPs, particularly pamidronate, appear to show promise in the symptomatic treatment of the bone pathology that occurs in SADHO, CRMO, and DSO of the mandible

Use of BPs in Orthopedic Implants

- The most common causes of orthopedic implant failure are
  - aseptic loosening around the implant stem that is often the result of micromotion and peri-implant osteolysis
  - a foreign body reaction that results in macrophage release of bone-resorbing cytokines by macrophages after phagocytosis of particulate wear debris.
- Limited clinical studies have shown the benefit of BPs in decreasing periprosthetic bone loss after uncemented hip and knee arthroplasties
- BPs have also been shown to decrease the inflammatory bone resorption that

occurs secondary to particle debris in several in vivo studies

Conclusion

- The ability of BPs to decrease bone turnover may make them useful compounds in the primary or adjunctive treatment of several conditions in this review
- Future investigations are needed to determine the potential role that BPs might play in the treatment of bone degeneration disease

題號	題目
1	下列何者非Bone pathology的疾病? (A) Osteogenesis imperfecta (B) Paget's disease of bone (C) Central giant cell granuloma (D) Granular cell tumors
答案(D)	出處：Oral & Maxillofacial Pathology p.437&p.533
題號	題目
2	下列何者非McCune-Albright syndrome的臨床表徵? (A) Polyostotic FD (B) Odontogenic keratocyst (C) Melanotic pigmentations (Café-au-lait macules) (D) Endocrine abnormalities (precocious puberty)
答案(B)	出處：Oral & Maxillofacial Pathology p.555&p.598