Medication related osteonecrosis of the jaws (MRONJ): Diagnosis and treatment

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General Introduction and Aim of this thesis

GENERAL INTRODUCTION

After its first description in 2003, Bisphosphonate related osteonecrosis of the jaws (BRONJ) became one of the most debated side-effects of an anti-resorptive drug[1]: a serious complication that still plagues several clinicians. It had serious consequences for the patients, who could suffer years of pain and sequestration and even loss of parts of the jaws. In 2008 the first cases of denosumab osteonecrosis of the jaw were reported[2, 3], another anti-resorptive drug, as well as anti-angiogenic inhibitors, such as sunitimib or bevacizumab, related osteonecrosis of the jaws (ONJ) and it became apparent that more drugs could induce this clinical picture[4]. Therefore, since 2014 the term medication related osteonecrosis of the jaws (MRONJ) was adopted[4]. The proper treatment is still discussed throughout the literature.

But is MRONJ a new disease? Its clinical features strongly resemble the so-called "phossy jaw" which was already described in nineteenth century[5-9]. During that age a clinical picture of (severe) inflammation with sequestration and lyses of jaw bone with (sometimes excessive) subperiosteal bone formation was reported; the "phossy jaw". This clinical picture strongly resembles the current clinical presentation in all forms of MRONJ.

Historical overview

Phossy Jaw

In the nineteenth century the phossy jaw as seen in figures 1 and 2 was a major problem, leading to the loss of jaw bone and sometimes even leading to death[8]. It was noticed that patients had been exposed to phosphorus fumes. These phosphorus fumes were inhaled in the matches or fireworks industry. In these industries yellow phosphorus was frequently used for ignition.

Figure 1 Phossy Jaw - Left mandible of 19th century male aged 26-35 years at death with bone changes suggesting possible phossy jaw. London Museum

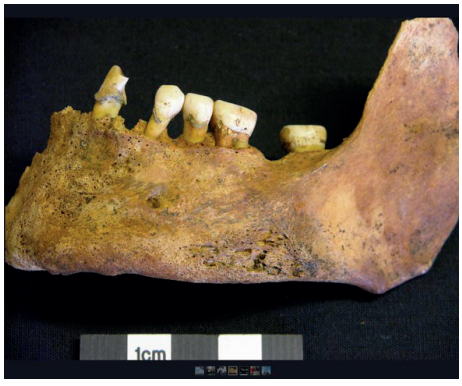


Figure 2 Phossy Jaw – Huntarian Museum - Odontologic Museum, Royal College of Surgeons, in London, England.

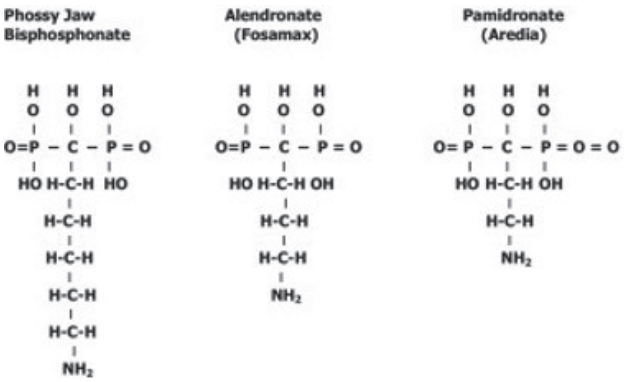
Therefore strike-anywhere-matches became very popular and the industry was flourishing. Employees inhaled phosphorus fumes (P_4O_{10}) and this lead to a chemical reaction in the body although the precise mechanism has not been fully elucidated. One hypothesis was that inhaled phosphorus has a chemical reaction with water, carbon dioxide (CO2) and lysine, a common amino acid in the body, which leads to the formation of a diphosphonate (fig 3) which chemical structure is almost identical to that of bisphosphonates[5].

The combination of phosphorus exposure and poor dental hygiene caused a clinical picture with striking resemblance to the disease currently known as MRONJ. After the association with yellow phosphorus became clear, its use was forbidden in 1906. However, reports of this so-called "phossy jaw" were published until the early sixties[7].

Bisphosphonates

Bisphosphonates were already developed in the 19th century. Originally, they were developed for non-human use in the textile, fertilizer and oil industries. In irrigation systems they were also used to soften water. In 1968 their potential use in disorders of bone metabolism was reported[10]. It was observed that the bisphosphonate prevented the dissolution of hydroxy apatite, and thus was capable of arresting bone resorption. The non-nitrogen containing bisphosphonates Etidronate and Clodronate were developed. These showed evident decrease in osteoclastic resorption in vitro as well as in vivo[11-13]. After these reports bisphophonates have been widely investigated as a potential treatment for osteoporosis, bone metastases and metabolic bone disease[14].

Figure 3 Chemical formula phossy jaw BP compared to alendronate and pamidronate (Marx[5])



Current use of anti-resorptive therapy

Bisphosphonates (BP) and denosumab (Dmab) are anti-resorptive agents that are being used in the treatment of various conditions such as osteoporosis (OP), bone metastases, multiple myeloma (MM) and Paget's disease. They inhibit osteoclast activity and thus bone resorption. In this thesis the use of anti-resorptive treatment in osteoporosis, metastatic bone disease and MM will be predominantly discussed.

Osteoporosis (OP)

Osteoporosis is a condition where there is a decrease in bone mass and bone structure leading to increased bone fragility. In the treatment of OP BP's are often described as weekly oral formulations or yearly zoledronic acid. Dmab is given in a dose of 60mg every 6 months.

Metastatic bone disease

In the case of to the bone metastasized solid malignancies, some of these metastases may cause local pain and hypercalcemia with accompanied complaints such as nausea, vomiting, fatigue. Inhibition of bone resorption will correct the hypercalcemia and will reduce pain. Strengthening of the bone with anti-resorptive medication may also prevent pathological fractures. Both bisphosphonates and denosumab can be used as treatment for these indications. Although dosages will be higher and more frequent then in OP, for instance oral formulations are hardly used and Dmab 120mg or Zoledronic acid is given monthly.

Anti-resorptive therapy might also be used as neoadjuvant therapy in e.g. breast cancer.

Multiple myeloma (MM)

In the case of MM, a malignancy of the plasma cells in the bone marrow, anti-resorptive treatment consisting of predominantly iv BP's, are part of the standard treatment since MM often presents with lytic bone lesions, hypercalcemia and pain. MM cells also produce osteoclast activating and osteoblast inhibiting factors.

Dosages anti-resorptive therapy

Due to the high turnover of bone in malignancies the dosage for this indication is higher than for osteoporosis, despite the medication.

Mechanism of action

Bisphosphonates

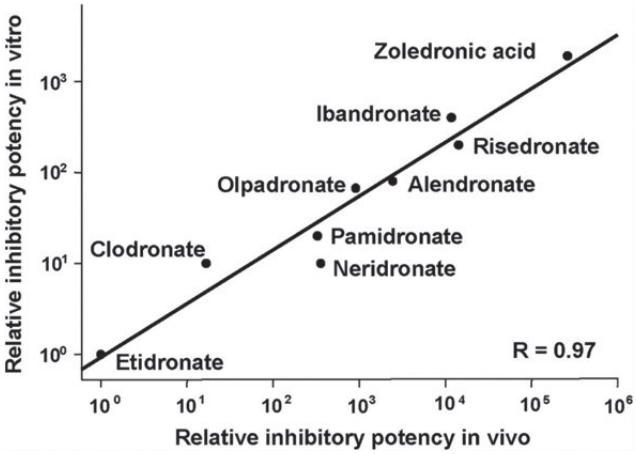
Pyrophosphates are a by-product of cell metabolism (hydrolysis of ATP) and inhibit bone mineralization. When an oxygen-atom of pyrophosphate is replaced by a carbon-atom, pyrophosphate, a diphosphate, changes to a bisphosphonate (BP). BP's have a higher affinity for bone than diphosphonates and the BP is bound to the hydroxy apatite with a larger affinity. Due to this competitive binding, BP's inhibit bone resorption. The addition of nitrogen-chains to the bisphosphonate will provide a covalent binding with the bone mineral. This defines the potency of the bisphosphonate to bind to bone. The potency is expressed in numbers compared to the "weakest" non-nitrogen BP etidronate, which has a potency of 1. Nitrogen containing BPs start with a potency of 100 (pamidronate) to >10.000 zoledronic acid (fig 4).

Nowadays, only nitrogen containing bisphosphonates are used. Because of their attachment to bone, they have a long half-life of several years and will stay active for years after administration of the medication.

The osteoclast is responsible for the resorption of bone. Bisphosphonates inhibit formation and the activity of osteoclasts[15, 16]. Bisphosphonates cause dysfunction by preventing adhesion of osteoclasts to bone matrix and by inducing early apoptosis with inhibition of bone resorption as a result[17, 18].

During the years more potent BP's have been developed, starting from the non-nitrogen containing BP etidronate, which has the lowest affinity to bone, to the zoledronic acid which has the highest affinity and is the most powerfull nitrogen containing BP.

Figure 4 Potency N-BP Adapted from Aapro M et al 2007[19]



Denosumab

Denosumab is an RANK-L inhibitor and therefore interacts on a different level with osteoclasts compared to bisphosphonates. RANK-L is necessary for activation of osteoclasts and maturation of preosteoclasts to osteoclasts. Denosumab binds RANK-L causing immediate cessation of the osteoclast and preosteoclast function and therefore inhibition of bone resorption. Unlike BP's, the effect of denosumab is temporary, and after several months osteoclast activity will re-start. Recent literature shows this could even result in a rebound in bone metabolism with bone markers increasing above baseline markers and subsequent increased fracture[20-22].

Osteonecrosis of the jaws (ONJ)

In 2003 a serious side effect of bisphosphonates was reported by Robert E. Marx[1]. He reported 36 patients presenting with osteonecrosis of the jaw(s) (ONJ) combined with pain, dental ab-

scesses, denuded bone (also in edentulous patients) and osteomyelitis. Removal of teeth often initiates exposed non-healing extraction sockets, although he also reported spontaneous occurrence of necrosis. Since then various cases have been described (ref) but the exact aetiology remains unknown. Some authors suggest a spontaneous "inside-out" origin, where they claim spontaneous disease starting in the jaw bone and then extending into the oral cavity[23-34]. Other authors report dental "outside-in" origins in which the disease starts after a dental extraction or treatment, from dental pathology, placement of implants or pressure sores with edentulous patients[35-38]. Osteonecrosis has also been reported after the use of Denosumab[2-4, 39, 40].

ONJ has an incidence of only 0,04-0,186%[40], which is relatively low, although the incidence may vary in patient groups.

Clinical features

Because of the variety of anti-resorptive agents causing ONJ, the American Association of Oral & Maxillofacial Surgeons decided to change the term: Bisphosphonate related osteonecrosis of the jaws[41, 42] to Medication related osteonecrosis of the jaws[4]. This disease was described as:

- Current or previous treatment with antiresorptive or antiangiogenic agents
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws

Patients may present with a variety of symptoms (fig 5-9). Most patients experience complaints of pain, swelling, foetor, exposed bone, pus discharge intra- or extraorally and/or neurosensory disturbances. They may even lose teeth or have undergone extraction of teeth or other dental surgical procedures such as implants. Sometimes symptoms have started with periodontal diseases or pressure sores in edentulous patients.

Figure 5 Extraoral submental fistula with pus discharge

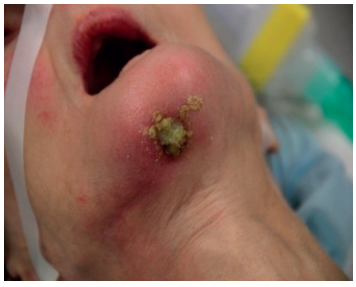
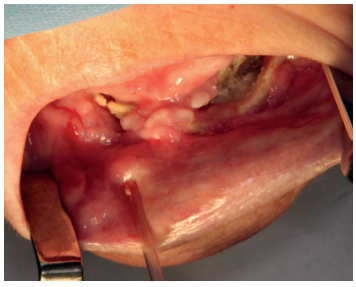
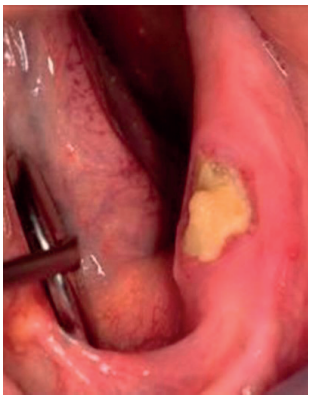


Figure 6 Intraoral view with denuded bone and fistula of the mandible



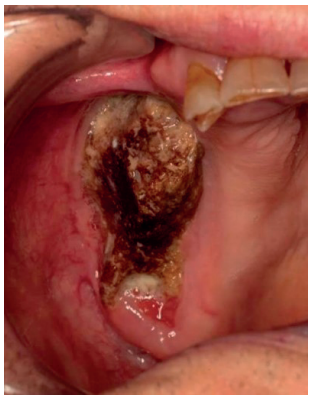
In addition stages (0-III) are defined based on the severity of the disease.

Figure 7 Stage 2 MRONJ in the lower left quadrant



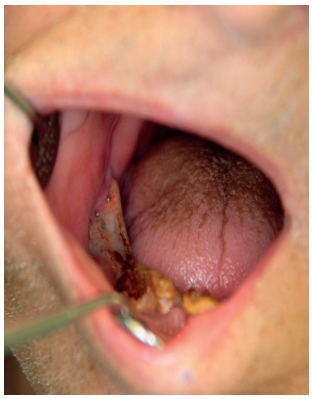
Stage 2

Figure 8 Stage 3 MRONJ in the upper right quadrant



stage 3

Figure 9 Stage 3 MRONJ in the lower right quadrant



stage 3

Table I: Rugierro SL et al Position paper AAOMS update 2014[4]

Stage	Clinical symptoms*	Treatment recommendations#
At risk	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates	No treatment indicated patient education
0	No clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms	Systemic management, including use of pain medication and antibiotics
1	Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection	Antibacterial mouth rinse clinical follow-up on a quarterly basis patient education and review of indications for continued bisphosphonate therapy
2	Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage	Symptomatic treatment with oral antibiotics oral antibacterial mouth rinse pain control debridement to relieve soft tissue irritation and infection control
3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and ≥1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor	Antibacterial mouth rinse antibiotic therapy and pain control surgical debridement or resection for longer-term palliation of infection and pain

* Exposed or probable bone in the maxillofacial region without resolution for longer than 8 weeks in patients treated with an antiresorptive or an antiangiogenic agent who have not received radiation therapy to the jaws.

Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should be considered because it is unlikely that extraction will exacerbate the established necrotic process.

Radiographic findings

Imaging in ONJ patients starts with the usual panoramic radiograph (PR)[43, 44]. The PR gives an impression of a lesion and its extent in 2D. Chronic use of anti-resorptive drugs may show the findings as mentioned in the updated Position Paper from 2014, as shown in table II.

Table II Radiological findings adapted from Ruggiero 2014 position paper update[4]

Radiological findings*
Alveolar bone loss or resorption not attributable to chronic periodontal disease
Changes to trabecular pattern—dense bone and no new bone in extraction sockets
Regions of osteosclerosis involving the alveolar bone or surrounding basilar bone
Thickening or obscuring of the periodontal ligament (thickening of the lamina dura, sclerosis, and decreased periodontal ligament space)

Panoramic radiographs (fig 10-13)

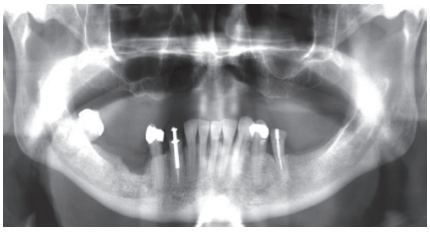


Figure 10 Panoramic radiograph: Stage 2 MRONJ: lysis in the right alveolar process in the region of the 45. Sclerosis is visible in the right mandibular body (the alveolar nerve canal is more lucent and the bone marrow is more opaque in comparison to the left side).

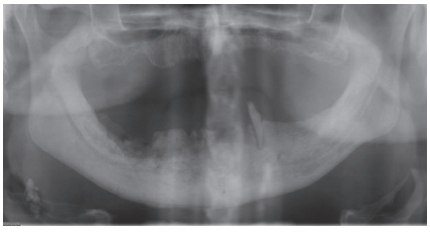


Figure 11 Panoramic radiograph Stage 2 MRONJ: severe lysis in 4th quadrant with sequesters. Subperiosteal bone is visible at the inferior border. There is substantial sclerosis with a lucent alveolar nerve canal and the wall of the contralateral canal is thickened.

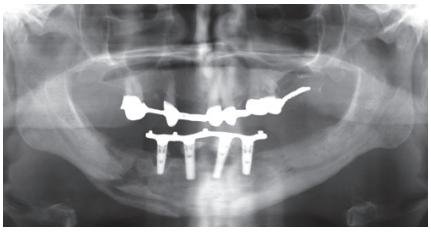


Figure 12 Panoramic radiograph Stage 3 MRONJ: Severe peri-implantitis around the 4 implants with horizontal and vertical bone loss, osteolysis and sequestra throughout the mandibular body extending to the inferior border. Subperiosteal bone formation is visible.

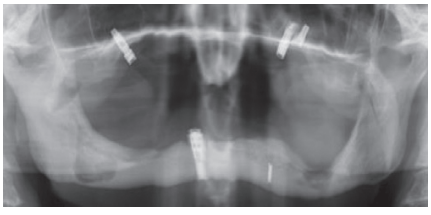


Figure 13 Panoramic radiograph Stage 3 MRONJ: Severe lysis and sequestra bilateral in the mandible with involvement of the inferior border.

For a more detailed examination (CB)CT is necessary. (CB)CT provides more information on the extent of the disease, involvement of nerves, sinuses, inferior border of the mandible and pathological fractures in advanced cases. Furthermore a scan is important in the planning of possible surgery.

Radiological findings on (CB)CT for bisphosphonate related osteonecrosis of the jaws have been well defined. These include thickened lamina dura, sclerosis, subperiosteal bone formation, sequestra, a pronounced inferior alveolar canal and discontinuation of the cortical border of the jaw(s)[43, 45-52].

Figure 14 Sequestrum

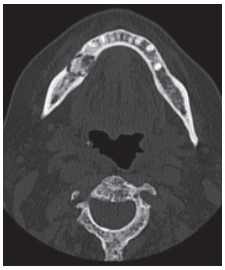


Figure 15 Subperiosteal bone

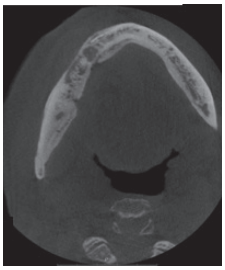


Figure 16 Lysis cortical border

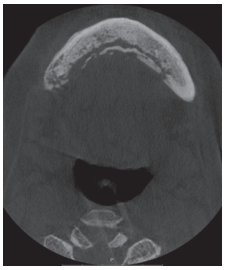
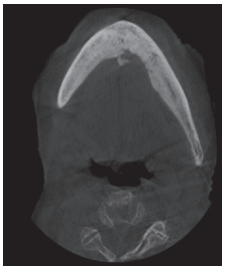


Figure 17 Sclerosis



Treatment

The optimal treatment strategy for ONJ has been debated extensively since the first report in 2003[1]. In the beginning a conservative approach was promoted[23, 24, 41, 42]. This meant treatment with antibiotics and mouth rinses. In severe cases, when there was a fracture or involvement of sinus or inferior border, a resection was performed with or without (free flap) reconstruction. However, in time a more predominantly European approach reported success with a relatively simple surgical technique in combination with the use of antibiotics[53-55]. This procedure consisted of a thorough sequestrectomy, often with saucerization and rounding off of sharp edges, and had success rates of 80-100%. Nevertheless controversies remained and international guidelines based on the AAOMS still promote conservative treatment with antibiotics and mouth rinses in the first 2 stages of MRONJ. Intervention in these stages would in their opinion lead to deterioration of the disease or development of further necrosis. From stage III surgical intervention with resection of the mandible with a microvascular flap reconstruction, an extensive procedure, is advised.

In conclusion etiology and treatment of MRONJ remain topics of discussion. But just as widely discussed are the surgical techniques stated above. These controversies have large effects on the treatment outcome of patients. Should or can a surgeon perform extensive surgery in an often vulnerable and fragile population? Or is successful treatment also possible while using a less

aggressive approach? Further evaluation of the differences in outcome will help to reach more consensus on treatment of this disease. Therefore further studies into cause, treatment and prevention of this disease are needed.

The aim of this thesis is to provide more insight in the diagnosis of MRONJ and the optimal treatment and intends to provide guidance for (dental) practitioners.

Outline of the thesis

PART I of this thesis will focus on the diagnosis of MRONJ, the origin(s) of MRONJ and possible risk factors.

CHAPTER 2 is a retrospective analysis on the precipitating factors for development of MRONJ in 45 patients. All possible (dental) events leading to complaints were studied.

CHAPTER 3 addresses the risks for MRONJ when there are implants involved in the necrosis. We retrospectively analysed our cohort for the relation between the implant and the development of MRONJ.

CHAPTER 4 is an observational pilot study on the findings on (cone beam) computed tomography ((CB)CT) regarding denosumab or bisphosphonate necrosis in 34 patients. The differences on several known characteristics of osteomyelitis are compared in order to assess possible differences in radiological presentation of both entities.

CHAPTER 5 illustrates the first case of denosumab necrosis of the jaws in the LUMC.

PART II focuses on treatment with a special emphasis on surgical treatment of MRONJ-patients.

CHAPTER 6 addresses the outcome of our surgical technique in 74 stage II/III-patients with bisphosphonate necrosis at the LUMC.

CHAPTER 7 is a retrospective analysis on the surgical results of a series of 11 patients with denosumab necrosis.

CHAPTER 8 shows the retrospective analysis of the treatment results of pathologic fractures of the mandible in 15 stage III MRONJ patients.

CHAPTER 9 assesses the surgical technique of the LUMC treatment protocol.

CHAPTER 10 shows a patient with severe stage III MRONJ in the mandible, in whom, due to excessive reactive subperiosteal bone formation around the jaw, the continuity was preserved after removal of all diseased bone.

In CHAPTER 11 a general discussion on this thesis is presented. CHAPTER 12 and 13 are summaries of the thesis in English and Dutch.

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