Recent clinical evidence in bisphosphonate-related osteomyelitis of the jaw: focus on risk, prevention and treatment.

Running title: Recent clinical evidence in bisphosphonate-related osteomyelitis of the jaw

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Abstract

Bisphosphonates (BPs) are widely used for the treatment of a range of conditions involving bone, such as osteoporosis and bone metastases of cancer, and their efficacy has been confirmed. Nevertheless, a first case of bisphosphonate-related osteonecrosis of the jaw (BRONJ) as an adverse effect of BP treatment was reported in 2003, and several clinical studies since then have elaborated the risk, prevention and treatment of BRONJ or bisphosphonate-related osteomyelitis of the jaw (BROMJ). However, effective decision making on BP risk is hampered by a lack of accurate information for patients, physicians or dentists. Furthermore, the narrow definition of BRONJ used to date has precluded the wider development of clinical research on risk.

In this review, we discuss current issues in BROMJ, with a focus on risk, prevention and treatment. In particular, we reconsider the definition of BRONJ from the standpoint of clinical evidence. Finally, we propose a new strategy for the treatment of BROMJ.

Key Words

Absolute risk, Bisphosphonate, Osteonecrosis of the jaw, Prevention, Prognosis, Relative risk, Risk factors, Treatment

Introduction

Bisphosphonate (BPs) are widely used for the prevention and treatment of a range of bone conditions, including postmenopausal osteoporosis, Paget disease, hypercalcemia in malignancies, and osteolytic bone metastases of cancer or multiple myeloma [1, 2]. BPs can be administered orally and intravenously in a wide range of doses, dosing intervals, and duration of administration [1]. The biologic action of BPs is to suppress farnesyl pyrophosphate synthase in the mevalonate biosynthetic pathway and inhibit the resorption of bone via the inactivation of osteoclasts [3]. Although this action accounts for the preventive or therapeutic efficacy of these agents, it also accounts for their uncommon skeletal-related events (SRE) or adverse effects [1, 2]. In particular, cases of osteonecrosis of the jaw (ONJ) have been reported as possible adverse effect of BPs since 2003 [4]. This condition is presently defined by the presence of exposed bone in the maxillofacial region for six to eight weeks [5-10], and patients with ONJ often encounter difficulties in sustaining their quality of life (QOL) [11].

Due to a lack of information, BP-related ONJ (BRONJ) was initially considered difficult to treat, similarly to osteoradionecrosis of the jaw, and to be a largely different condition to osteomyelitis of the jaw (OMJ) [4, 12, 13]. Regrettably, however, a number of organizations, national regulatory agencies, medical specialty societies and clinicians disseminated information on the risk of BPs for ONJ without accurate data on incidence, risk factors, prognosis, or treatment [14], and thereby confounded both patients treated with BPs and medical and dental professionals. Many relevant studies and reviews have since appeared, however, and these early problems have been progressively resolved.

In this paper, we review clinical studies of BRONJ or BP-related OMJ (BROMJ) over the last 10 years, outline the problems identified, and then discuss current issues in BRONJ and BROMJ, with a focus on risk, prevention and treatment. In particular, we discuss the definition of BRONJ from the standpoint of clinical evidence. Finally, we propose a new strategy for the treatment of BROMJ.

Methods

Literature search strategy and research questions

A systematic search of the English literature was conducted. The MEDLINE/PUBMED and Scopus databases were searched from January 1, 2003 to December 31, 2012. In the MEDLINE search, we entered the following Medical Subject Headings (MeSH): "diphosphonates"[MeSH Terms] OR "diphosphonates"[All Fields] OR "bisphosphonate"[All Fields] OR "bisphosphonate-associated osteonecrosis of the jaw"[MeSH Terms] OR "bisphosphonate-associated"[All Fields] AND ("jaw"[MeSH Terms] OR "jaw"[All Fields]) AND (hasabstract[text] AND "humans"[MeSH Terms] AND English[lang])). We additionally searched studies published from January 1, 2012 to December 31, 2012 in the Scopus database by using the following key words: (TITLE-ABS-KEY-AUTH("osteonecrosis of the jaw" OR "osteomyelitis of the jaw" OR "inflammation of the jaw") AND (LIMIT-TO(PUBYEAR,2012)) AND (LIMIT-TO(LANGUAGE, "English")).

Titles and abstracts were reviewed to determine relevance. The search for clinical evidence included randomized controlled trials (RCT), cohort studies, case-control studies, cross-sectional studies, case series and literature reviews. Letters, animal studies and basic studies were excluded.

Our research questions in the review were as follows:

1. How much of the absolute risk of BROMJ is estimated to be accounted for by users of intravenous BPs?
2. How much of the absolute risk of BROMJ is estimated to be accounted for by users of oral BPs?
3. How much of the relative risk of OMJ is estimated by the incidence of OMJ in BPs users compared to non-users, regardless of BP type?
4. What are the risk factors of BROMJ?
5. Are there any prognosis markers for the incidence of BROMJ?
6. Are there any effective preventive measures for the incidence of BROMJ?
7. Are there any effective treatments for BROMJ?
8. Are there any new treatments for BROMJ?

In the review, we investigated the following information: year of electronic publication, country, setting, type of study, target population and number, main endpoint, diagnostician, type of BP, search procedure of BPs, risk index, risk ratio, risk factors, prognosis, and treatments. In addition, the evidence grade of studies

was classified according to the 2010 American Heart Association guideline [15]. Here, we define meta-analyses as evidence 1a, RCTs as 1b, cohort studies as 2, and case-control studies as 3.

A unit of incidence rates was converted into the unit “per million person-years”. All statistical analyses were performed using Stata 11.2 software (Stata Corporation, College Station, TX, USA).

Results and Discussion

Definition of epidemiological terms

To aid understanding of this literature review, we first explain the epidemiological terms cumulative incidence, prevalence, incidence rate, absolute risk and relative risk, as follows.

Cumulative incidence refers to the number or proportion of a group (cohort) of people who experience the onset of a health-related event during a specified time interval [16]. In contrast, prevalence refers to the total number of individuals who have an attribute or disease at a particular time or particular period divided by the population at risk of having the attribute or disease at that time or midway through the period, respectively [16]. Although the term "prevalence" is thus inherently different from "cumulative incidence" in meaning, we include "prevalence" in "cumulative incidence" here because of the severely limited number of cross-sectional studies identified in the literature review. In contrast, incidence rate refers to the rate at which a new event occurs in a population, and is quite different from "cumulative incidence". Accordingly, we distinguish the term "incidence rate" from "cumulative incidence" in the review [16].

These risks are then grouped as "absolute risk", which means the number of events in a group divided by the total number of subjects in that group [16]. Moreover, we use the term "relative risk" to evaluate the risk of BPs for OMJ. This means the ratio of the risk of an event among the exposed to that among the unexposed [16].

History and Definitions of BROMJ

In 2003, Marx first suggested a possible association between the use of intravenous BPs and avascular necrosis of the jaw [4], and described 36 patients receiving pamidronate or zoledronate who had exposure of necrotic bone in the oral cavity. Since this sensational report, hundreds of cases of BRONJ cases have been reported [17-30] and a number of clinical studies published between 2003 and 2006 demonstrated the absolute risk or risk factors of BRONJ among patients using intravenous BPs [31-38]. In the same period, the manufacturers or the US Food and Drug Administration indicated the presence of a safety concern regarding the use of BPs [14]. Furthermore, some expert panels recommended the prevention and treatment of BP-associated ONJ notwithstanding that evidence for the association was limited, particularly among users of oral BPs [19, 20, 39-41]. Finally, in 2007, a position paper by the American Association of Oral

and Maxillofacial Surgeons (AAOMS) proposed the establishment of BRONJ as a new disease entity with the following three characteristics: 1) current or previous treatment with a bisphosphonate; 2) exposed, necrotic bone in the maxillofacial region that has persisted for more than 8 weeks; and 3) no history of radiation therapy to the jaw [42]. Following this position paper, several associations stated definitions of BRONJ, BP-associated ONJ, or BP-ONJ which, despite the differences in naming, were commonly defined by the presence of exposed bone in the maxillofacial region [5-10, 43].

Here, we propose grouping cases of OMJ together with ONJ, because we consider it difficult to distinguish ONJ from OMJ, for two reasons: first, radiographic findings in infected jawbone in patients treated with BPs are similar to those in BP-induced ONJ even if necrotic bone cannot be clinically visualized [44-46]; and second, the presence of osteonecrosis is a common histopathologic finding in both BP-induced ONJ and OMJ [47]. These finding suggest that the condition of bone exposure in the oral cavity is not always caused by avascular necrosis of the jaw. Several studies or reviews have also regarded ONJ as the same as OMJ [48-51]. We therefore need to reconsider the definition of "BRONJ" according to this recent clinical evidence and pathological findings of the condition; in particular, such early identification of OMJ without long-term exposure of necrotic bone may be relevant to treatment.

How much of the absolute risk of BROMJ is estimated to be accounted for by users of intravenous BPs?

Accumulated evidence has clarified that the risk of BROMJ is higher in patients taking intravenous BPs than oral BPs [37, 52-54]. In addition, most patients receiving intravenous BPs were considered to have cancer [7] and be at higher risk for infectious disease than those taking oral BPs. We therefore discuss incidence by route of administration.

Table 1 show characteristics of the literature concerning cumulative risk of BROMJ among patients taking intravenous BPs. A total of 91 papers describing the cumulative risk of BROMJ were identified [10, 31, 32, 34-37, 49, 53-135], the largest number of which came from the US, followed by Italy, Greece and other countries. Most studies were conducted in hospitals, and were aimed at investigating the cumulative incidence or risk factors of BROMJ. More than half of the 91 studies were cohort studies, although almost none of these had a control group, in other words patients who were not treated with BPs. Further, 21 of the 91 studies were conducted as RCTs, but with efficacy of BPs or SREs as main outcome, and the

incidence of BROMJ as a secondary endpoint only. The cumulative incidence of BROMJ in those studies ranged from 0% to 51.8%, or the incidence rate ranged from 0.70 per 100 patients to 5.5 per 1,000 person-years.

We summarized the characteristics of studies of BROMJ among patients taking intravenous BPs which had an evidence level of 3 or better (Table 2 and 3). The cumulative incidence of BROMJ in multicenter RCTs was extremely low, ranging from 0% to 3.5%, with a median incidence of 0.6% (Table 2). In contrast, the cumulative incidence of BROMJ in controlled, observational studies ranged from 0.34% to 14.8%, with a median incidence of 5.0% (Table 3). These findings appear to indicate a large difference between these studies in absolute risk.

We speculate that the difference in absolute risk between studies is partly due to differences among the investigators of BROMJ in the various studies. In particular, the diagnostic criteria for BROMJ or the background of those diagnosing BROMJ was unclear in prospective studies because BROMJ was just one SRE or secondary endpoint. This might have resulted in underestimation of the incidence of BROMJ. In addition, we suspect that differences in the settings or target populations of the studies mainly influenced absolute risk; in other words, participants in the clinical trials may have been generally healthier than the subjects of the clinical observational studies. On the other hand, the subjects in clinical observational studies may have had several primary illnesses and required substantial medical treatment, including BPs. Moreover, differences between these studies may have resulted from differences in the duration of exposure to BPs, although we were unable to investigate duration in detail. To sum up, any interpretation of our results should be done with due regard to study design, setting, target population, sample size, definition of outcome, and diagnostician.

Denosumab is a human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand. Several studies have shown the superiority of this agent to BPs in the treatment of bone metastases and prevention of SRE in cancer patients [105, 111, 112, 119, 134]. Notably, these studies have also indicated that denosumab has a similar risk for OMJ as BPs. The absolute risk of OMJ was estimated to range from 0.8% to 2.3%. Given that evidence for the risk of OMJ with denosumab remains limited, however, particular vigilance against the possibility of adverse effects in these patients is required.

How much of the absolute risk of BROMJ is estimated to be accounted for by users of oral BPs?

The cumulative incidence of BROMJ in patients taking oral BPs ranged from 0% to 7.8% [10, 37, 51, 54, 62, 106, 136-150], or the incidence rate ranged from 6.3 to 366 per million person-years [53, 146, 151, 152]. We abstracted those studies with an evidence level of 3 or better (Table 4), among which cumulative incidence was estimated to range from 0% to 4.3%, or the incidence rate from 6.3 to 366 per million person-years.

Due to the low occurrence of BROMJ in patients treated with oral BPs, initial studies estimated incidence by anticipating the total number of individuals who had been prescribed oral BPs [62, 144]. More recently, however, population-based or larger hospital-based studies, as well as administrative data have allowed an understanding of the absolute risk of BROMJ in patients taking oral BPs [51, 53, 106, 146, 151, 152]. From these studies and our previous study, the cumulative risk of OMJ with oral BPs is less than 1% in patients with osteoporosis, and the incidence risk is considered to be low.

How much of the relative risk of OMJ is estimated by the incidence of OMJ in BPs users compared to non-users, regardless of BP type?

A meta-analysis which extracted data from 15 RCTs (n = 10,694) showed that treatment with zoledronic acid was significantly associated with the occurrence of ONJ (M-H pooled odds ratios (OR) = 3.2, 95% confidence interval (CI), 1.7–8) compared with no use [98]. In contrast, a meta-analysis of other data extracted from three RCTs (n = 736) showed no significant association between intravenous BPs and ONJ (pooled relative risks (RR) = 4.0, 95% CI, 0.44-35.8) [2]. Six observational studies reported the relative risk of BROMJ in patients treated with intravenous BPs while 10 observational studies reported the risk in patients treated with oral BPs (Table 5). The estimated OR, RR or hazard risks in patients treated with intravenous BPs ranged from 1.6 (95% CI, 0.71-3.8) to 299.5 (95% CI, 70-1282). Of these studies, only one found no significant association between intravenous BPs and OMJ [118], whereas the rest showed an increased risk of OMJ with intravenous BPs, with significance [37, 49, 52-54, 153]. Similarly, four studies found no significant or inverse association between oral BPs and OMJ [37, 53, 54, 154], whereas the rest showed an increased risk of OMJ with oral BPs, ranging from 2.2 (95% CI, 1.2-4.3) to 15.5 (95% CI, 6.0-38.7) [50, 51, 146, 151-153]. Overall, both intravenous and oral BPs may increase the risk of OMJ, although

these studies slightly differed in endpoint characteristics (e.g. OMJ or Jaw surgery code), sample size, target population and number, and presence of adjustment for confounding. A conclusive answer awaits additional meta-analysis or larger clinical observational studies.

What are the risk factors of BROMJ?

More than one hundred studies have examined risk factors associated with BROMJ or prognosis. In particular, diabetes, cancer chemotherapy, corticosteroids, and thalidomide have all been suggested to be risk factors [31, 35, 50, 51, 53, 56, 60, 63, 70, 75, 86, 87, 110, 125, 128, 146, 153, 155-165]. Unfortunately, however, most of these studies evaluated risk factors without adjustment for confounding factors or controls, which may have introduced bias into judgment or decision-making. We therefore summarized the possible risk factors for BROMJ in controlled studies with consideration to potential confounding factors (Table 6).

Most studies have shown that BPs with high potency or prolonged duration/no. of cycles increase the risk of BROMJ. These findings may be supported by the dose-response or strength association and coherence. On the other hand, findings for the association between other possible risk factors and BROMJ lack consistency. For example, some studies found an association between other possible risk factors such as use of cancer chemotherapy and BROMJ [50, 56, 60, 161], whereas others did not [54, 63, 70, 75, 110, 153, 158, 160, 162]. Similarly, associations between other demographic factors such as sex, age or race and BROMJ are also controversial. With regard to oral status, many studies reported that the use of a denture, severe periodontal status, and surgical dental treatments such as tooth extraction may be risk factors of BROMJ, whereas others showed no significant association between periodontal status, caries, or root canal treatment and BROMJ. Overall, almost all these factors were investigated as possible confounding factors or secondary endpoints in the studies, but given that some surveys were conducted using questionnaires, interview, or chart review, and most definitions of factors were not described in detail, the accuracy of some diagnoses might have been low. In addition, many studies may have had insufficient statistical power to evaluate risk factors for BROMJ. These results should therefore be interpreted with care. Larger, well-designed controlled studies targeting factors involved in or associated with the induction of BROMJ are required.

Are there any prognosis markers for the incidence of BROMJ?

C-terminal telopeptide (CTX) and other bone markers such as N-terminal telopeptide (NTX) or bone-specific alkaline phosphatase (BAP) were first reported as possible prognostic markers of BROMJ in 2007 [166]. Our review process identified seven relevant studies appearing since then [145, 167-173]. Among these, however, three studies were characterized as case series without controls [166-168] and the rest were case-control studies without adjustment for confounding factors [145, 169-173]. We were therefore unable to find sufficient evidence to support the hypothesis that suppression of CTX, NTX, BAP or other bone makers was a prognostic marker of BROMJ. One possibility is that although local bone turnover in the jaw might be suppressed, this local turnover has no impact on biochemical markers which reflect systemic bone turnover [172].

With regard to genetic factors, nine studies have identified differences in genetic polymorphisms in case-control studies, and shown associations between some genes and the risk of BROMJ [73, 174-181]. These results suggest that the risk of BROMJ is increased by genes encoding for cytochrome P450 and aromatase, as well as RBMS3, IGFBP7, ABCC4, COL1A1, RANK, MMP2, OPG, OPN, CYP2C8, and NFAT2. These genes, which are associated with drug or bone metabolism, are possible prognosis markers of BROMJ, albeit that sample sizes in these studies were low [179, 180].

Are there any effective preventive measures for the incidence of BROMJ?

A drug holiday from BPs has been reported to prevent BROMJ [5, 7]; in particular, one study found that a three-month washout period before surgical treatment prevented the incidence of BROMJ [166]. Here, however, we found no clinical evidence to support this hypothesis. Biologically, BPs are considered to accumulate in skeletal sites that have active bone remodeling, and to remain there for a long time [9, 47, 152]. Present knowledge therefore provides little evidence to support the use of a three-month drug holiday to wash-out BPs from skeletal sites, and to support its clinical efficacy in the prevention of BROMJ.

Several reports investigated the effectiveness of oral care in the prevention of BROMJ [77, 82, 83, 182, 183]. Although these studies were all conducted in single centers and did not consider other confounding factors, they nevertheless had sufficient sample sizes to examine the hypothesis, and all showed significant risk reductions by interventional preventive oral care. Although direct evidence that the severity of oral

hygiene or periodontal status increases the incidence of BROMJ remains limited [54, 162, 184], these reports suggest that poor oral hygiene and a severe periodontal status are risk factors for BROMJ and that dental care prevents the incidence of BROMJ.

Are there any effective treatments for BROMJ?

Table 7 summarizes controlled studies which aimed to evaluate the treatment of BROMJ [79, 171, 185-191]. Almost all studies demonstrated that surgical treatment was effective [186, 188-191]: while they differed in surgical treatment method, indications, and target populations, they all showed a common relationship between the presence of preoperative inflammation and prognosis of BROMJ, and found that successful treatment was more frequent when antibiotic therapy and/or oral care was provided before surgery. These results suggest that the control of local inflammation plays a crucial role in ensuring a positive prognosis for BROMJ after surgical treatment.

One RCT showed that hyperbaric oxygen (HBO) therapy was effective for the treatment of BROMJ, as judged by a decrease in lesion size, number, and pain, and improvement in QOL [185]. Unfortunately, however, this study did not have a sufficient sample size (n = 49) to allow for adjustment of confounding factors. Two mechanisms for this effectiveness have been proposed. First, the produced reactive oxygen and nitrogen species signal osteoclast differentiation, activity and viability. Second, HBO therapy ameliorates edema and inflammation, augments microbial killing and invokes stem cell mobilization, vasculogenesis and tissue repair in other wounds [185]. Further large, well-designed controlled studies to investigate the effectiveness of surgical treatment or HBO therapy are required.

Are there any new treatments for BROMJ?

Recent studies have reported that parathyroid hormone (teriparatide) is effective in in patients with BROMJ [192-198]. One of these studies was a case report and the rest were case series, however, and their level of clinical evidence was accordingly insufficient to confirm this efficacy. Interestingly, these studies did confirm the presence of bone regeneration in inflammatory regions at more than 2 months after subcutaneous injection of teriparatide into patients with BROMJ. The ongoing accumulation of case reports and case-series, or stronger evidence, might allow a better understanding of the pathogenesis of BROMJ

and a new approach to its treatment.

Our proposal for the diagnosis, prevention and treatment of BROMJ in the early stage

From the accumulated clinical evidence in this review, we propose the following diagnosis, prevention and treatment strategy for BROMJ in the early stage (Figure 1). Compared to the AAOMS's strategy in 2009 [7], the four hierarchical diagnostic criteria defined below allow OMJ to be identified earlier, without the need for long-term exposure of necrotic bone [51]:

1. possible cases are diagnosed by increased uptake on technetium bone scan with characteristic signs and symptoms of bone infection, and/or findings on dental panoramic X-ray.
2. probable cases are diagnosed by imaging findings on computed tomography or magnetic resonance imaging scans which are consistent with findings of possible cases.
3. confirmed cases are diagnosed by a histological picture consistent with OMJ and/or the isolation of microorganisms in samples obtained by extraoral open surgery, percutaneous biopsy of bone, excised bone or intramedullary tissue, or pus aspiration from adjacent tissues, with findings of probable cases
4. cases which do not meet the above criteria are not considered as cases of OMJ.

Diagnosis of OMJ is often difficult, however, particularly in the early stage [199], and these criteria are not always consistently applied to different stages of OMJ. Osteomyelitis is caused by a certain inciting focus that enables the infection to propagate but has various clinical expressions, and the clinical characteristics and laboratory features of infection are not always present [199, 200]. This background explains why diagnostic imaging has long played a major role in the investigation of suspected osteomyelitis [201]. CT or MRI scans were of greater value in diagnosing OMJ than technetium bone scans or plain radiographs, but the highest priority was given to a histological picture consistent with OMJ and/or the isolation of a microorganism in samples [199-201].

The early identification of BROMJ using objective imaging or histological findings might also enable the use of more aggressive treatment, such as HBO therapy or surgical treatment if indicated, which might in turn lead to a better treatment response.

Conclusions

We conducted a systematic review of previous clinical studies of BROMJ over 10 years with a focus on risk, prevention and treatment. The still-accumulating evidence suggests that all types of BP increase the risk of OMJ incidence. Prevention of BROMJ might be aided by oral care before and after BP administration. Once a symptomatic condition in the jaw occurs, however, the use of technetium bone scan and CT or MRI findings may be useful in evaluating the condition in its early stage. After local inflammation is controlled with antibiotic therapy and/or oral care, surgical treatment may be valid. Biological and interventional studies suggest that HBO may be a useful adjunctive therapy during the disease course in encouraging bone remodeling and wound healing. Further investigations of the prevention and treatment of BROMJ in larger, prospective, well-designed controlled studies are required.

List of Abbreviations

AAOMS, American Association of Oral and Maxillofacial Surgeons; BAP, bone-specific alkaline phosphatase; BPs, bisphosphonates; BROMJ, bisphosphonate-related osteomyelitis of the jaw; BRONJ, bisphosphonate-related osteonecrosis of the jaw; CI, confidence interval; CTX, C-terminal telopeptide; HBO, hyperbaric oxygen; NTX, N-terminal telopeptide; OMJ, osteomyelitis of the jaw; ONJ, osteonecrosis of the jaw; OR, odds ratios; QOL, quality of life; RCT, randomized controlled trial; RR, relative risks; SRE, skeletal-related events.

Conflicts of interests

All authors declare that there are no financial relationships with any organizations that might have an interest in the submitted work and no other relationships or activities that could appear to have influenced the submitted work.

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Figure legend

BPs = bisphosphonates; HBO = hyperbaric oxygen.

Figure 1: Propose diagnostic criteria for OMJ

Figure 1.

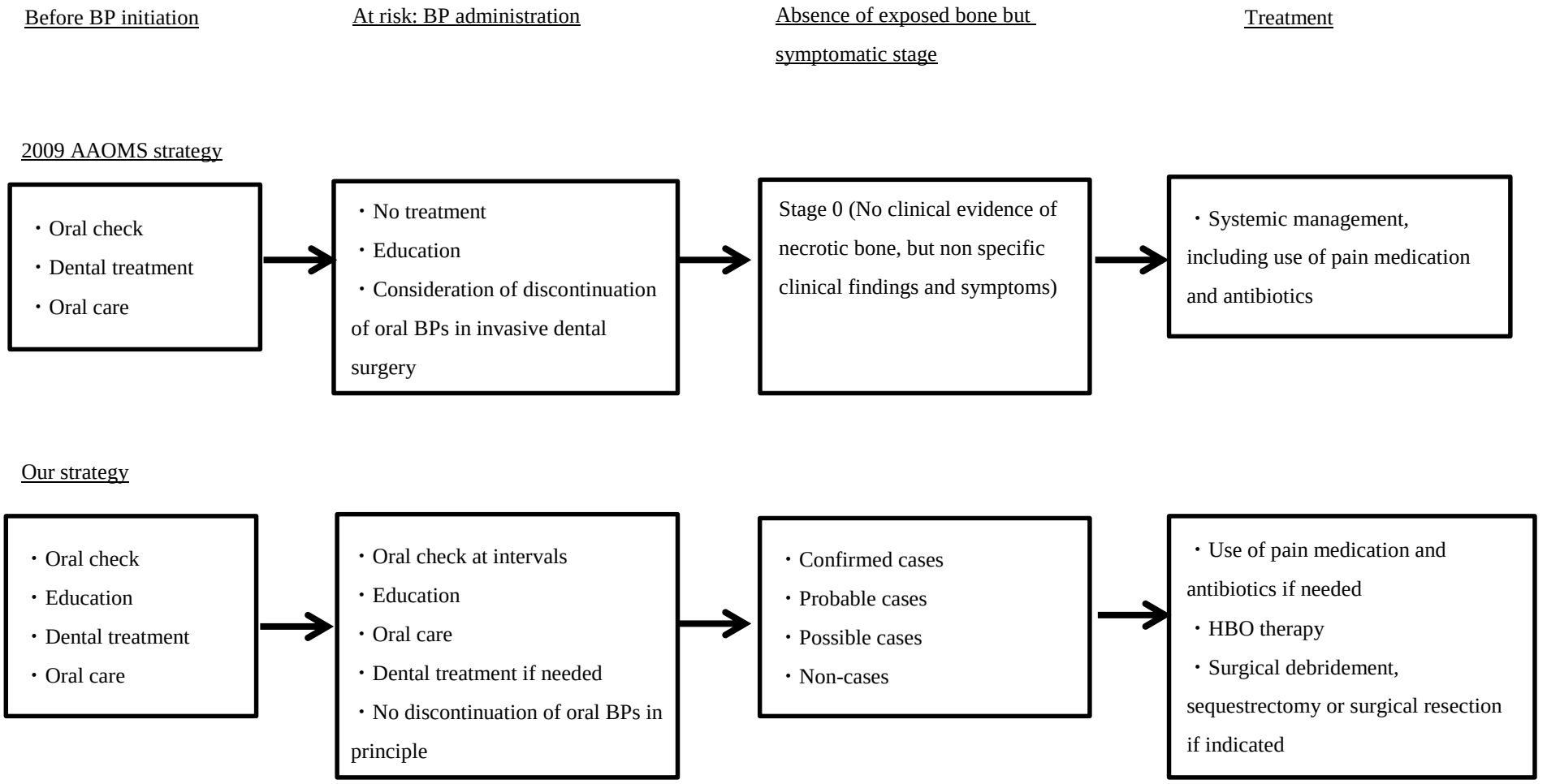
Before BP initiation
At risk: BP administration
Absence of exposed bone but symptomatic stage
Treatment
2009 AAOMS strategy
・Oral check
・Dental treatment
・Oral care
・No treatment
・Education
・Consideration of discontinuation of oral BPs in invasive dental surgery
Stage 0 (No clinical evidence of necrotic bone, but non specific clinical findings and symptoms)
・Systemic management, including use of pain medication and antibiotics
Our strategy
・Oral check
・Education
・Dental treatment
・Oral care
・Oral check at intervals
・Education
・Oral care
・Dental treatment if needed
・No discontinuation of oral BPs in principle
・Confirmed cases
・Probable cases
・Possible cases
・Non-cases
・Use of pain medication and antibiotics if needed
・HBO therapy
・Surgical debridement, sequestrectomy or surgical resection if indicated

Table 1. Characteristics of studies of cumulative risk of bisphosphonate-related osteomyelitis of the jaw among patients taking intravenous bisphosphonates

Published year	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
No. of studies	0	0	2	4	14	18	14	9	17	13

Country	USA	Italy	Greece	International	Germany	Canada	Australia	Japan	Others
No. of studies	24	18	8	7	6	4	4	3	19

Setting	Hospital	Multi-center	Single-center*	Health insurance data	Population-based	Others
No. of studies	55	20	6	6	2	2

Type of study	Meta-analysis	RCT	Cohort	Cohort w/o control	Case control	Cross-sectional
No. of studies	1	21	5	59	2	3

Target population	BC	MM	PC	LC	Cancer complex	Osteoporosis or Paget disease	Others
No. of studies	18	15	8	2	37	5	6

No. of population	<100	100-500	500-1000	1000-5000	5000>
No. of studies	28	28	10	15	10

Main endpoint	BROMJ	SRE including BROMJ	Codes of surgery or inflammation of the jaw
No. of studies	47	39	5

Diagnostician	Surgeons or oncologists	Dentists	Physicians	Investigators or committee	Others	Unclear

No. of studies	35	17	3	14	2	20

Search procedure	From pharmacy or prescription records	From medical or dental records	Marketing information
No. of studies	79	9	3

Evidence grade	1a (meta-analysis)	1b (RCT)	2 or 3 (controlled study)	4 (quasi-experimental study)
No. of studies	1	21	7	62
publication lists	98	61, 69, 72, 80, 93, 96, 101, 104, 105, 108, 111-113, 115, 116, 119, 120, 122, 123, 134, 135	37, 49, 53, 54, 106, 118, 133	10, 31, 32, 34-36, 55-60, 62-71, 73-79, 81-92, 94, 95, 97, 99, 100, 102, 103, 107, 109, 110, 114, 117, 121, 124-132

BC = breast cancer; BPs = Bisphosphonate; BROMJ = bisphosphonate-related osteomyelitis of the jaw; LC = lung cancer; MM = multiple myeloma; PC = prostate cancer; RCT = randomized clinical trial; SRE = skeletal-related events; w/o = without.

* Studies were conducted in a single center, excluded hospitals.

Table 2. Incidence of bisphosphonate-related osteomyelitis of the jaw among patients taking intravenous bisphosphonates in studies with an evidence level of 1

No.	Author	Setting	Target	Kind of BP	End point*	Diagnosis	Outcomes/users	Incidence (%)	Evidence
98	Mauri	N.A.	BC	P, ZA, I, C, R	0	unclear	13/3,987	0.2	1a
61	Lyles	MC	HF	ZA	1	physicians	0/1,054	0.0	1b
69	Grbric	MC	OSP	ZA	1	AC	1/3,875	0.03	1b
72	Brufsky	MC	BC	ZA	1	unclear	0/1,652	0.0	1b
80	Musto	MC	MM	ZA	1	unclear	1/81	1.2	1b
93	Hines	SC	BC	ZA	1	OMS	1//274	0.4	1b
96	Brufsky	MC	BC	ZA	1	AC of ONJ	0/301	0.0	1b
101	Guarneri	MC	BC	P, ZA, C with BV	1	unclear	2/233-10/425	0.9-2.4	1b
104	Gimsing	MC	MM	P	1	questionnaire	30mg: 2/252, 90mg: 8/250	30mg: 0.8, 90mg: 3.2	1b
105	Stopeck	MC	BC	ZA, DMAB	1	AC of ONJ	ZA: 14/1,013, DMAB: 20/1,026	ZA: 1.4, DMAB: 2.0	1b
108	Morgan	MC	MM	ZA, C	1	dentists	ZA: 35/983, C: 3/979	ZA: 3.5, C: 0.3	1b
111	Henry	MC	CA, MM	ZA, DMAB	1	AC of ONJ	ZA: 11/878, DMAB: 10/878	ZA: 1.3, DMAB: 1.1	1b
112	Fizazi	MC	PC	ZA, DMAB	1	AC	ZA: 12/945, DMAB: 22/943	ZA: 1.2, DMAB: 2.3	1b
113	Coleman	MC	BC	ZA	1	investigators	11/1,590	0.7	1b

115	Gnant	MC	BC	ZA	1	investigators or patients level	0/900	0.0	1b
116	Pivot	SC	BC	I	1	investigators or patients level	2/334	0.6	1b
119	Saad	MC	CA, MM	ZA, DMAB	1	AC of dental experts	ZA: 37/2,836, DMAB: 52/2,841	ZA: 1.3, DMAB: 1.8	1b
120	Brufsky	MC	BC	ZA	1	investigators and AC of ONJ	0/602	0.0	1b
122	Coleman	MC	BC	ZA	1	investigators	17/1,686	1.1	1b
123	Safra	SC	BC	ZA	1	investigators	0/47	0.0	1b
134	Scagliotti	MC	LC	ZA, DMAB	1	unclear	ZA: 3/406, DMAB: 3/395	ZA: 0.7, DMAB: 0.8	1b
135	Scagliotti	MC	LC	ZA	1	investigators	1/226	0.4	1b

AC = adjudication committee; BC = breast cancer; BPs = bisphosphonates; BV = bevacizumab; C = clodronate; CA = cancer patients; DMAB = denosumab; HF = hip fracture patients; I = ibandronate; LC = lung cancer; MC = multicenter; MM = multiple myeloma; N.A. = not applicable; OMS = oral and maxillofacial surgeons; ONJ = osteonecrosis of the jaw; OSP = osteoporosis; P = pamidronate; PC = prostate cancer; R = risedronate; SC = single center; ZA = zoledronic acid.

* Endpoint 0 means ONJ and 1 means skeletal related events including ONJ.

Table 3. Incidence of bisphosphonate-related osteomyelitis of the jaw among patients taking intravenous bisphosphonates in studies with an evidence level of 2 or 3

No.	Author	Setting	Target	Kind of BP	End point*	Diagnosis	Outcomes/ BPs users	Incidence (% or rate)	Evidence
37	Zavras	HIP	CA, MM	P, ZA	2	ICD-9 code	20/5,850	0.34	2
53	Tennis	HIP	CA	I, P, ZA	0	ICD-9 or CPT and chart review	15/2,876	5.3 per 1,000 person-years	2
54	Yamazaki	HOSP	CA	INC, P, ZA	0	OMS	4/27	14.8†	2
106	Skrepnek	HIP	CA, OSP	P, ZA	2	ICD-9 code	CA: 12/6,276, OSP: 21/2,321	CA: 0.43 OSP: 0.90	2
133	Beuselinck	HOSP	RCC	ZA	1	patient level	5/49	9.6	2
49	Wilkinson	HIP	CA	P, ZA	2	ICD-9 code	95/14,349	5.5 per 100 patients	3
118	Baillargeon	HIP	OSP	E, I, P, ZA	2	ICD-9 code	9/2,296	0.70 per 100 patients	3

BPs = bisphosphonates; CA = cancer patients; CPT = current procedural terminology; E = etidronate; HIP = health insurance plan data; HOSP = hospital; I = ibandronate; INC = incadronate; ICD = international classification of diseases; MM = multiple myeloma; OMS = oral and maxillofacial surgeons; OSP = osteoporosis; P = pamidronate; RCC = renal cell carcinoma patients; ZA = zoledronic acid.

* Endpoint 0 means osteonecrosis of the jaw (ONJ), 1 means skeletal related events including ONJ, and 2 means jaw surgery or inflammation of the jaw code.

† Cumulative incidence of bisphosphonate-related osteonecrosis of the jaw after tooth extraction.

Table 4. Incidence of bisphosphonate-related osteomyelitis of the jaw among patients taking oral bisphosphonates

No.	Author	Setting	Target population	Kind of BP/ Route of BP administration	End point*	Diagnosis	Outcomes/ BPs users	Incidence (% or rate)	Evidence
138	Wells	N.A.	PW	A	1	review of RCTs	N.A.	0	1a
139	Wells	N.A.	PW	R	1	review of RCTs	N.A.	0	1a
136	Jeffcoat	HOSP	OSP, OSPE	A	1	dentists	0/355	0	1b
149	Paterson	MC	BC	C	1	investigators	1/1,662	0.06	1b
37	Zavras	HIP	CA	A, R	2	ICD-9 code	19/20,438	0.092	2
51	Yamazaki	HOSP	OSP	A, E, R	3	ICD-10 and OMS chart review	21-46/4,129	0.46-0.99	2
53	Tennis	HIP	OSP	A, E, I, R	0	ICD-9 or CPT and chart review	2/6,319	150 per million person-years†	2
54	Yamazaki	HOSP	OSP	A, E, R	0	OMS	1/99	1.0‡	2
106	Skrepnek	HIP	CA, OSP	A, E	2	ICD-9 code	79/213,364-199/213,364	0.02-0.09	2
141	Sedghizadeh	HOSP	PT taking A	A	0	dentists	9/208	4.3	2
146	Fellows	HIP	HP, KPNW	PO	0	ICD-9 and chart review	6/21,163	6.3 per million person-years†	2
151	Etminan	HIP	OSP	A, E, R	2	ICD-9 code	196/87,837	267 per million person-years	3

152	Lapi	BEST	OSP	PO	2	ICD-9 and chart review	61/65,220	366 per million person-years†	3

A = alendronate; BEST = Bisphosphonates Effectiveness Safety Trade-off network; BC = breast cancer; BPs = bisphosphonates; C = clodronate; CA = cancer patients; CPT = current procedural terminology; E = etidronate; HIP = health insurance plan data; HP = Health Partners of Minnesota; HOSP = hospital; KPNW = Kaiser Permanente Northwest; I = ibandronate; ICD = international classification of diseases; MC = multicenter; N.A. = not applicable; OMS = oral and maxillofacial surgery; OSP = osteoporosis; OSPE = osteopenia; PO = per os; PT = patients; PW = postmenopausal women; R = risedronate; RCT; = randomized clinical trial.

* Endpoint 0 means osteonecrosis of the jaw (ONJ), 1 means skeletal related events including ONJ, 2 means jaw surgery or inflammation of the jaw code, and 3 means osteomyelitis of the jaw.

† To convert an incidence rate to “per million person-years,” we simply multiplied.

‡ Cumulative incidence of bisphosphonate-related ONJ after tooth extraction.

Table 5. Relative risk of bisphosphonates for osteomyelitis of the jaw

No.	Author	Setting	Target population	Route of BP administration	End point*	Population no.	Risk index	Risk ratio [95% CI]	Adjust-ment	Evidence
49	Wilkinson	HIP	CA	IV	2	44,771	HR	11.5 [6.5-20.3]	yes	3
118	Baillargeon	HIP	OSP	IV	0	9,161	HR	1.6 [0.71-3.8]	yes	3
37	Zavras	HIP	CA	IV/PO	2	5,850	RR	IV: 4.2 [2.7-6.7]	no	2
								PO: 1.2 [0.7-1.8]		
52	Cartsos	HIP	CA	IV	2	714,217	OR	IV: 4.5 [3.2-6.3]	no	3
			OSP	PO				PO: 0.65 [0.54-0.79]		
53	Tennis	HIP	CA	IV	0	46,542	OR	IV: 8.8 [2.0-38]	yes	2
			OSP	PO				PO: 0.15 [0.00-0.36]		
54	Yamazaki	HOSP	TE	IV	0	3,216	RR	IV: 200.2 [23.8-1679]	yes	2
				PO				PO: 12.9 [0.82-204]		
153	Barasch	PBRN	CA+OSP	IV	2	764	OR	IV: 299.5 [70-1282]	yes	3
				PO				PO: 12.2 [4.3-35]		
50	Vestergaard	NR	OSP	PO	0	414,245	HR	A: 3.2 [1.4-6.9]	yes	3
								E: 2.2 [1.2-4.3]		
51	Yamazaki	HOSP	OSP	PO	3	6,923	OR	5.0 [1.9-12.9]	yes	2
146	Fellows	HIP	HP, KPNW	PO	0	572,606	OR	15.5 [6.0-38.7]	no	2
152	Lapi	BEST	OSP	PO	0	65,220	OR	2.8 [1.3-5.9]	yes	3
151	Etminan	HIP	OSP	PO	2	87,837	RR	A: 2.9 [1.7-5.1]	yes	3
								E: 2.4 [1.0-5.6]		

								R: 3.3 [1.0-10.6]		
154	Pazianas	HIP	OSP	PO	2	3,505	OR	0.91 [0.70-1.19]	yes	3

A = alendronate; BEST = Bisphosphonates Effectiveness Safety Trade-off network; BPs = bisphosphonates; CA = cancer patients; E = etidronate; HIP = Health Insurance Plan data; HOSP = Hospital; HP = Health Partners of Minnesota; HR = hazard risk; I = ibandronate; IV = intravenous; NR = national registry of Danish population; OR = odds ratio; OSP = osteoporosis; P = pamidronate; PBRN = practice based research network; PO = per os; R = risedronate; RR = relative risk; TE = patients undergoing tooth extraction; ZA = zoledronic acid.

* Endpoint 0 means osteonecrosis of the jaw (ONJ), 1 means skeletal related events including ONJ, 2 means jaw surgery or inflammation of the jaw code, and 3 means osteomyelitis of the jaw.

Table 6. Risk factors of bisphosphonate-related osteomyelitis of the jaw

Risk factor	Publication lists of controlled studies with adjustment for covariates	
	Positive association	Negative association
Gender	164	35, 49, 53, 54, 56, 60, 70, 71, 91, 100
Age	38, 165	31, 49, 53, 54, 56, 70, 71, 75, 91, 100, 164
Race	117, 165	
Smoking	125, 160	75, 91, 163
Alcohol	167	54, 75, 160
Primary illness		
Diabetes	50, 125, 156, 159	56, 128, 110, 146, 160
Hypertension		56, 160
Use of BPs		
Duration/cycle of BPs	31, 35, 36, 49, 57, 75, 91, 125, 153, 161, 164, 165, 168	50, 86, 87, 152, 154, 158
BPs with high potency	31, 35, 36, 38, 49, 50, 52, 54, 75, 91, 125, 160, 164, 181	154, 158
Use of other drugs		
Cancer chemotherapy	50, 56, 60, 161	54, 63, 70, 75, 110, 153, 158, 160, 162
Corticosteroids	172	53, 54, 56, 70, 86, 110, 125, 128, 153, 158, 160
Thalidomide	35	31, 70, 71, 86, 110
Oral status		
Tooth extraction	38, 70, 75, 91, 128, 153, 162, 163	
Periodontitis/Oral hygiene	54, 162	91,153, 159, 163
Use of denture	91, 163, 167	128, 165

BPs = bisphosphonates

Table 7. Treatment of bisphosphonate-related osteomyelitis of the jaw

ID	Author	Treatment	Setting	Target	Kinds of BP	Population no.	Improvements	Evidence
185	Freiberger	HBO therapy	REC	BRONJ	P, ZA, A	46	time to healing, pain, QOL	1b
79	Montefusco	antibiotic prophylaxis v.s. none	HOSP	MM	P, ZA	178	reduction of BRONJ incidence	2
171	Atalay	Laser-assisted v.s. conventional surgery	HOSP	BRONJ	ZA	20	no statistically significant difference between two surgeries	2
186	Wutzl	Surgical treatment	HOSP	BRONJ	P, ZA, A, I, R	58	stages after surgery	2
187	Gasparini	Spiramycin v.s. ACA	HOSP	BRONJ	unclear	25	clinical outcomes	2
188	Vescovi	Er:YAG laser surgery	HOSP	BRONJ	unclear	91	clinical outcomes	2
189	Vescovi	Surgical treatment	MC	BRONJ	P, ZA, A, others	567	clinical outcomes	2
190	Vescovi	Medical and surgical therapy	HOSP	BRONJ	unclear	128	clinical outcomes	2
191	Graziani	Surgical intervention	HOSP	BRONJ	P, ZA, A, C, I, N, R	347	clinical outcomes*	3

A = alendronate; ACA = amoxicillin and clavulanic acid; BPs = bisphosphonates; BRONJ = bisphosphonate-related osteonecrosis of the jaw; C = clodronate; E = etidronate; Er: YAG = erbium-doped yttrium aluminum garnet; HBO = hyperbaric oxygen; HOSP = Hospital; HR = hazard risk; I = ibandronate; IV = intravenous; MC = multicenter; MM = multiple myeloma; N = neridronate; P = pamidronate; PO = per os; QOL = quality of life; R = risedronate; REC = recruitment nationwide; ZA = zoledronic acid.

* The result was estimated by odds ratios adjusted for age, gender, stage, and use of corticosteroids.