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Osteoporosis and bisphosphonates-related osteonecrosis of the jaw: Not just a sporadic coincidence – a multi-centre study☆

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ABSTRACT

Introduction: Bisphosphonates (BPs) are powerful drugs that inhibit bone metabolism. Adverse side effects are rare but potentially severe such as bisphosphonate-related osteonecrosis of the jaw (BRONJ). To date, research has primarily focused on the development and progression of BRONJ in cancer patients with bone metastasis, who have received high dosages of BPs intravenously. However, a potential dilemma may arise from a far larger cohort, namely the millions of osteoporosis patients on long-term oral BP therapy.
Patients and methods: This current study assessed 470 cases of BRONJ diagnosed between 2004 and 2008 at eleven different European clinical centres and has resulted in the identification of a considerable cohort of osteoporosis patients suffering from BRONJ. Each patient was clinically examined and a detailed medical history was raised.
Results: In total, 37/470 cases (7.8%) were associated with oral BP therapy due to osteoporosis. The majority (57%) of affected individuals did not have any risk factors for BRONJ as defined by the American Association of Oral and Maxillofacial Surgery. The average duration of BP intake of patients without risk factors was longer and the respective patients were older compared to patients with risk factors, but no statistical significant difference was found. In 78% of patients the duration of oral BP therapy exceeded 3 years prior to BRONJ diagnosis.

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Discussion: The results from this study suggest that the relative frequency of osteoporosis patients on oral BPs suffering from BRONJ is higher than previously reported. There is an urgent need to substantiate epidemiological characteristics of BRONJ in large cohorts of individuals.

1. Introduction

Osteoporosis is a health threat of major public concern. Due to osteoporosis, approximately 50% of women and 20% of men over 50 years of age will suffer from a fragility fracture in their remaining lifetime (Sambrook and Cooper, 2006). Osteoporosis is effectively managed with bisphosphonates (BPs), an antiresorptive drug that can significantly prevent skeletal complications, in particular fractures (Berenson et al., 1996; Black et al., 1996, 2006; Cranney et al., 2002; Sambrook and Cooper, 2006). Side effects associated with BP intake are generally rare. However, since 2003 (Marx, 2003; Migliorati, 2003; Wang et al., 2003) bisphosphonate-related osteonecrosis of the jaw (BRONJ) has become a clinical problem of rising importance (Migliorati et al., 2006). BRONJ is defined by (i) transmucosal or trans-cutaneous jawbone exposure over a period of 8 weeks, (ii) a positive history of BP administration, and (iii) a negative history for irradiation of the head and neck region (AAOMFS, 2007; Khosla et al., 2007). It is frequently accompanied by a variety of other clinical manifestations such as pain, soft tissue swelling or ulceration, suppuration, intra- or extra-oral sinus tracks, abscess and impairment of nerve functions (Marx, 2003; Abu-Id et al., 2006, 2008; AAOMFS, 2007; Khosla et al., 2007) (Fig. 1). Therapy results of early stages are good (Markose et al., 2009; Otto et al., 2009; Pautke et al., 2009) in particular in cases with oral BP intake (Marx et al., 2007). However, if diagnosis or therapy is delayed, entire parts of the jawbones may have to be removed in severe cases which also necessitate a complex post-surgical rehabilitation (Engroff and Kim, 2007; Mücke et al., 2009; Pautke et al., 2010). This progression has almost exclusively been reported in cancer patients with bone metastasis who received intravenous BP therapy.

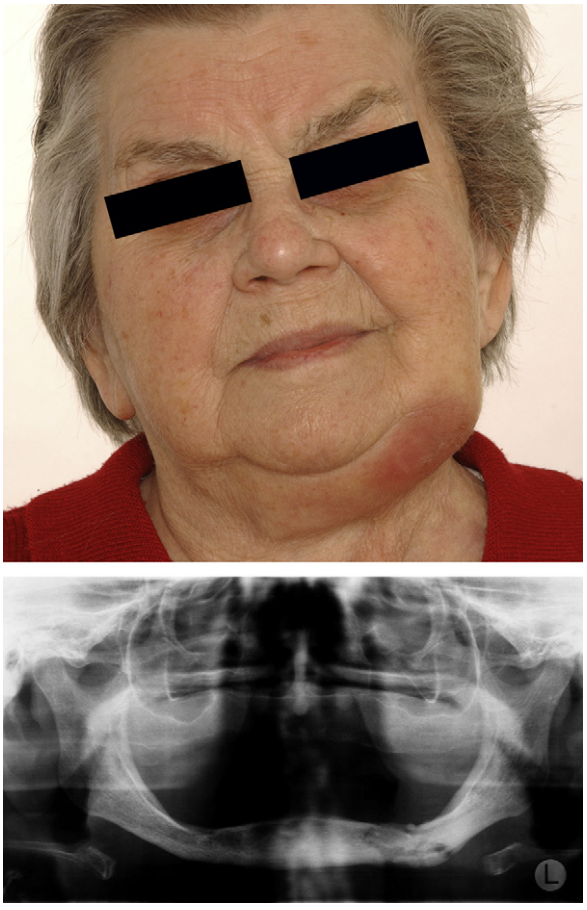

Fig. 1. Clinical picture and panoramic radiograph of a female patient suffering from an acute abscess due to BP-associated osteonecrosis of the left lower jaw under oral BP intake.

Several factors have been suggested to trigger an increased risk of the BRONJ manifestation (AAOMFS, 2007; Khosla et al., 2007), but concrete evidence has been limited to the duration of BP intake, the BP derivate and previous dental procedures (Bamias et al., 2005; Badros et al., 2006; Dimopoulos et al., 2009). Patients subjected to intravenous BP administration are at higher risk of developing a BRONJ with a prevalence of 3–18% (Bamias et al., 2005; Wang et al., 2007; Badros et al., 2008; Boonyapakorn et al., 2008; Kyrgidis et al., 2008; Walter et al., 2008). Preventive dental measures (Dimopoulos et al., 2009) as well as a modified dosing schedule (Corso et al., 2007) can reduce but not eliminate the risk. Dento-alveolar surgeries have been reported to precede a BRONJ manifestation in over 80% of the cases. As a consequence, elective surgical procedures, such as dental implant insertion are contraindicated in these patients (Piesold et al., 2006; Khosla et al., 2007; Ruggiero et al., 2009).

In contrast, studies concerning the risk of BRONJ among users of oral BPs are sparse, limited in total to approximately 200 cases (Abu-Id et al., 2006; Piesold et al., 2006; Marx et al., 2007; Yarom et al., 2007; Hess et al., 2008; King and Umland, 2008; Rizzoli et al., 2008; Hong et al., 2009). Therefore, the association between oral BPs and jaw necrosis has been regarded, by some, as being of negligible clinical significance. For example, neither the American Association of Clinical Endocrinologists (AACE, 2003), the National Osteoporosis Society (McLeod et al., 2007), nor the Joint Organization of the Scientific Societies of Osteology of Germany, Austria and Switzerland (DVO, 2006) provide a recommendation concerning elective invasive dental procedures (e.g. insertion of osteointegrated implants) in osteoporosis patients on oral BP. Moreover, when the issue is addressed, recommendations can be contradictory. The American Society for Bone and Mineral Research sees no contraindication in performing elective alveolar bone surgery in patients on oral BPs (Khosla et al., 2007) whilst the German Association of Oral and Maxillofacial Surgeons recommends to refrain from bone surgery during ongoing oral BP therapy (Piesold et al., 2006). Similarly, the American Association of Oral and Maxillofacial Surgeons, explicitly advises to perform invasive dental surgery only if no further risk factors exist when the BP intake exceeds 3 years (AAOMFS, 2007).

Overall, the association between oral BP and BRONJ has been largely neglected (Pazianas et al., 2007, 2008; Rizzoli et al., 2008) notwithstanding the characteristics of this large cohort of individuals. Current figures estimate that over 190 million prescriptions for oral BPs are dispensed worldwide each year (AAOMFS, 2007) and more than 15 million (elective) dental implants operations and other (necessary) dento-alveolar surgical procedures are performed worldwide.

This paper describes a large cohort of patients with osteoporosis who developed BRONJ in association with oral BPs. It aims to (i) examine the association between oral BPs and BRONJ and (ii) increase awareness among osteoporosis-treating physicians who

are in the position to monitor and specifically educate patients about preventive measures.

2. Patients and methods

This retrospective multi-centre study incorporates patients treated in eleven different clinical centres of Oral and Maxillofacial Surgery or Oral Medicine across Europe including Germany (University of Munich, Technical University of Munich, University of Kiel, University of Marburg, University of Bochum, Asklepios Hospital Hamburg), Austria (Landeskrankenhaus Feldkirch), Switzerland (University of Bern), Great Britain (London Eastman Dental Institute) and Italy (University of Palermo, Second University of Naples). Clinical data of patients diagnosed with BRONJ between January 2004 and April 2008 were collected and reviewed. Each patient in the study was thoroughly clinically examined and a detailed medical history was taken. Diagnostic criteria included (i) a history of current or previous exposure to BP medications, (ii) the presence of intra-oral or trans-cutaneous jawbone exposure, and (iii) no history of radiotherapy to the head and neck region (Khosla et al., 2007). Evidence of bone necrosis at histopathology was considered to be an adjunctive but not necessary criterion. Other causes of osteonecrosis were excluded by the medical history.

Further analysis focussed on individuals with osteoporosis and exposure to oral BPs. Data collected included typology, duration, dosage of BP therapy, presence and type of concomitant disease and medical therapies. The presence of concomitant risk factors such as cortisteroid therapy, diabetes, alcohol and smoking habits, and poor oral hygiene were also recorded (AAOMFS, 2007; Khosla et al., 2007). It is noteworthy, that evidence in patients on intravenous BPs has only been linked to the duration of BP intake, the BP derivate and the occurrence of previous dental procedures (Bamias et al., 2005; Badros et al., 2006; Dimopoulos et al., 2009). Due to the small number of patients no such correlations have been investigated in patients on oral BPs. Patients taking oral BP for indications other than osteoporosis were not included in this analysis.

Table 1
Admission diagnosis of osteoporosis patients with BRONJ ($n = 37$).

Mucosa lesion	2
Periimplantitis	2
Non-healing extraction socket	9
Fistula	4
Fracture	2
Abscess	3
Osteomyelitis	5
Pain	2
Osteonecrosis	8

2.1. Statistical analysis

Statistical differences between the duration of BP therapy and the age of patients were tested using the log-rank test, *t*-test, and Mann–Whitney-*U* test. Verification of equivalence of mean BP intake duration was performed using the 95% confidence interval of the deviation with a defined range of ±3 months. Deviations of the means were expressed as standard deviations.

3. Results

The data from 470 patients (female $n = 300$, male $n = 170$) diagnosed with BP-related osteonecrosis of the jaws (BRONJ) were collected. The vast majority of patients (425/470, 90.5%) received BP medication due to malignancy, including breast cancer (34%), multiple myeloma (33%), prostatic cancer (13%) and other carcinoma (10%). 45 patients (9.6%) suffered from BRONJ following the intake of BPs due to osteoporosis. Among these, 37 (7.8% of the entire patient pool) were treated with oral BP (female $n = 30$, male $n = 7$, mean age 68.7 years, age range 46–88 years). The admission diagnoses of the treating dentists were not used as criterion for inclusion in this study, as the medical history raised by the admitting dentists was often incomplete and the diagnoses varied widely (Table 1). Notably, only 22% of the patients were referred to the hospital with the correct diagnosis of BRONJ.

The presence of one or more BRONJ risk factors as defined by the American Society of Oral and Maxillofacial Surgery (AAOMFS, 2007) was identified in 16 of 37 patients (43%). Steroid intake was most prevalent ($n = 11/37$, 29.7%), followed by smoking, the intake of cytostatic drugs (both $n = 5/37$, 13.5%), and poor oral hygiene (1/37). Out of the 16 patients, 6 revealed two risk factors simultaneously ($n = 5$ steroid + cytostatic drug; $n = 1$ poor oral hygiene + smoking). Although not explicitly defined as an independent risk factor (AAOMFS, 2007), a BP therapy in excess of 3 years was identified in 29/37 patients (78%). Patients with BRONJ but with no concomitant risk factors were, on average, 6 years older than patients with risk factors, a difference that was, however, statistically not significant (*t*-test $p = 0.163$; Man–Whitney-*U* test $p = 0.206$) (Fig. 2).

The average duration of oral BP intake was 57.8 months (±5.3 months). The duration of therapy was 10 months longer in patients without risk factors (62.3 months ± 7.0) than in those with risk

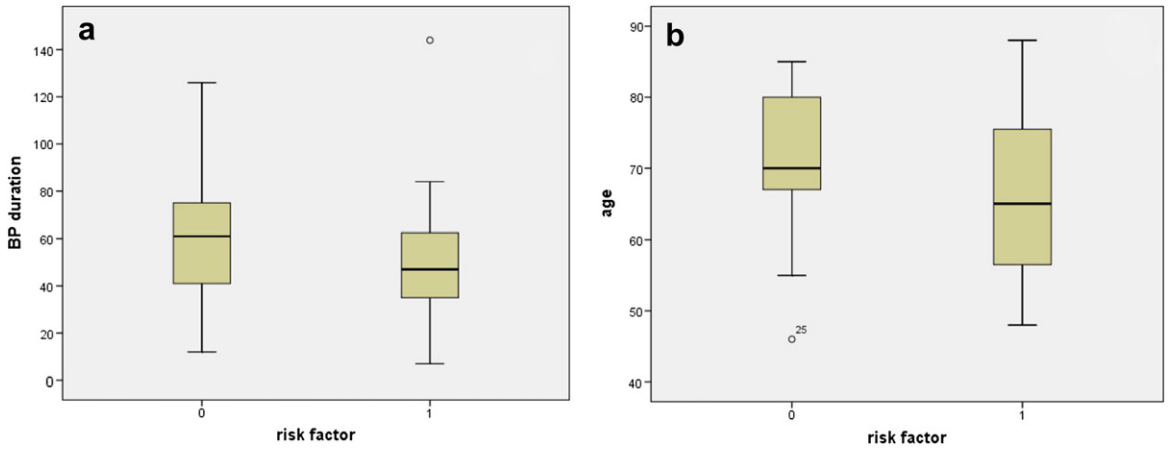

Fig. 2. Comparison of (a) duration of BP medication as well as (b) age of patients with (1) and without (0) risk factors suffering from BRONJ due to oral BP intake.

factors (52 month ± 8.1), a difference with no statistical significance (*t*-test ($p = 0.343$); Mann–Whitney-*U* test ($p = 0.254$)). The equivalence test could not identify a statistically significant correlation regarding the intake duration differences of 6 months (recommended discontinuation period when dento-alveolar procedures are impending).

The most frequent type of oral BP among osteoporosis patients with BRONJ was Alendronate ($n = 28$ or 75%), followed by Risedronate ($n = 4$ or 10%), Ibrandronate ($n = 3$ or 8%), Clodronate ($n = 1$ or 2.7%), and a combination of two (first Risedronate then Alendronate ($n = 1$ or 2.7%)).

4. Discussion

BPs are widely used in patients with osteoporosis in order to prevent bone fractures (Sambrook and Cooper, 2006). As the incidence of BRONJ is several magnitudes higher in cancer patients receiving intravenous, rather than oral, BPs, the clinical significance of BRONJ in osteoporosis patients may be under-estimated by clinicians and research institutions. This is underlined by the controversy and contradictions regarding preventive measures and recommendations released by various groups of experts, and drug manufacturers. Because the life expectancy of osteoporosis patients is significantly longer than cancer patients with bone metastasis, a detailed investigation of individuals on oral BPs is timely. The progression of BRONJ in osteoporosis patients has the potential to represent a significant long-lasting burden in terms of quality of life and consumption of resources.

The duration of a BP therapy has been demonstrated to be a significant risk factor for the BRONJ development (Bamias et al., 2005; Badros et al., 2006) in cancer patients. Although oral BPs are less bio-available than intravenous formulations, they are used over extended periods (as confirmed in the present study where the mean duration of therapy was 4.8 years). It is conceivable that, though less bio-available, the extended duration of oral intake may act as a risk factor of BRONJ (AAOMFS, 2007). Indeed, the mean duration of intravenous BPs intake is significantly lower in BRONJ patients (3.3 years) (Bamias et al., 2005; Dimopoulos et al., 2006). While the unlimited use of BPs in cancer patients is currently being discussed (Kyle et al., 2007; Badros et al., 2008), this is also a critical issue that is relevant to osteoporosis patients. In this context, the FLEX study (Fracture Intervention Trial Long-term Extension) analyzed the effects of discontinuing an oral alendronate therapy in postmenopausal woman that have been previously treated over five years (Black et al., 2006). A control group received placebo over the next five years, while the treatment group was continuously provided with BPs. Placebo treatment resulted only in moderate decrease of hip and spine bone mineral density (BMD) and a gradual increase in bone turnover markers compared to a continued therapy with BPs. While clinically recognized vertebral fractures increased after discontinuation, the cumulative risk of non-vertebral fractures and morphometric vertebral fractures remained unchanged. However, the absolute risk of both clinical vertebral and non-vertebral fractures was greatest in patients with additional known fracture risk factors. Based on these findings, *Black* et al. concluded that a discontinuation of a therapy with BPs after five years does not lead to a significantly increased fracture risk in most patients. Therefore, a prolonged therapy beyond five years should be considered for patients with high risk of clinical vertebral fracture, such as those with very low BMD or history of vertebral fracture (Black et al., 2006). In FLEX particular attention has been paid to the monitoring of a decrease in BMD. This examination, possibly amended by additional assessment of bone turnover markers, would be appropriate for all patients where therapy has been discontinued. It is worth mentioning, that alendronate despite its low bioavailability of less than 1% in oral applications is a very potent nitrogen-containing BP (Berenson et al., 2002). However, recently the cases of osteonecrosis of the jaw have also been described in other osteoclast inhibitory drugs, namely receptor activator for NF-κB ligand (RANKL) inhibitors (Taylor et al., 2009; Aghaloo et al., 2010). Further multi-centre studies are needed to evaluate, whether the risk for the development of an osteonecrosis of the jaw is generally increased in osteoporosis patients.

To minimize the risk of BRONJ, some have suggested the discontinuation of oral BPs ("drug holiday") when dental treatment is impending (Piesold et al., 2006; AAOMFS, 2007; Marx et al., 2007; Yarom et al., 2007). This is, however, not supported by any evidence. The precise duration of pathological effects of BPs awaits to be elucidated as bone turnover markers remain suppressed for several years following the discontinuation of BP treatment (Chavassieux et al., 1997; Bone et al., 2004; Sambrook and Cooper, 2006). Recently a new parameter predicting the risk of osteonecrosis of the jaw in patients who require oral surgery under ongoing BP treatment has been postulated, namely serum C-telopeptide cross-link of type 1 collagen (sCTX) (Marx et al., 2007). However, the value of CTX as a predictive marker of ONJ has not yet been proven in clinical trials and there is hardly any clinical data supporting the use of a sCTX threshold in order to minimize the risk of BRONJ in patients receiving oral BP treatment (Baim and Miller, 2009).

To date, approximately 200 cases of BRONJ have been reported to be directly linked to oral BP (Ruggiero et al., 2004; Marx et al., 2005, 2007; Farrugia et al., 2006; Pazianas et al., 2007; Yarom et al., 2007; Hess et al., 2008; Rizzoli et al., 2008; Hong et al., 2009; Silverman and Landesberg, 2009) and epidemiologic data are sparse. A recent cohort study reported a prevalence of 0.1% (Lo et al., 2010). Although it would be good clinical practice to design a case control study, prospective data are very difficult to obtain. Therefore more reliance should be placed on retrospective data (Khosla et al., 2007). Indeed, the present study describes this large cohort of patients and substantiates the association between oral BPs and osteonecrosis of the jaws. We are able to corroborate the notion that BRONJ far more associated with an intravenous BPs application in patients suffering from cancer (90% of the reviewed cases) and report that 7.8% of all patients with BRONJ were on oral BP therapy due to osteoporosis. This relative proportion is higher than previous indications which ranged from 0.02% to 5.8% (King and Umland, 2008; Rizzoli et al., 2008; Silverman and Landesberg, 2009). Only 43% of the cases analyzed showed the presence of one or more risk factors of BRONJ, suggesting that the majority would have been considered to be low risk patients. In line with a previous report (Marx et al., 2007), 57% of patients in this study suffered from spontaneous BRONJ. The findings of the present study highlight that individuals with one or more risk factors of BRONJ tend to be younger and have a shorter duration of BP therapy than patients with spontaneous BRONJ. Even though the difference was statistically not significant, these data may indicate that individuals without additional risk factors are not protected from BRONJ development.

5. Conclusion

This study confirms the association between oral BPs and jaw osteonecrosis in individuals with osteoporosis. There is an urgent need for further investigations aimed at clarifying epidemiological characteristics and preventive measures of BRONJ. We suggest considering the intake duration of oral BPs in excess of 3 years to be classified as an independent risk factor when elective dento-alveolar surgeries are impending, a notion that should be taken into account when designing a prospective case control study.

References

AACE: American Association of Clinical Endocrinologists: medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis, http://www.aace.com/pub/pdf/guidelines/osteoporosis2001Revised.pdf, 2001 Edition, with selected updates for 2003

AAOMFS: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. J Oral Maxillofac Surg 65: 369–376, 2007

Abu-Id MH, Acil Y, Gottschalk J, Kreusch T. Bisphosphonate-associated osteonecrosis of the jaw. Mund Kiefer Gesichtschir 10: 73–81, 2006

Abu-Id MH, Warnke PH, Gottschalk J, Springer I, Wiltfang J, Acil Y, Pa Russo, Kreusch T: "Bis-phossy jaws" – high and low risk factors for bisphosphonate-induced osteonecrosis of the jaw. J Craniomaxillofac Surg 36: 95–103, 2008

Aghaloo TL, Felsenfeld AL, Tetradis S: Osteonecrosis of the jaw in a patient on Denosumab. J Oral Maxillofac Surg 68: 959–963, 2010

Badros A, Terpos E, Katodritou E, Goloubeva O, Kastritis E, Verrou E, Zervas K, Mr Baer, Meiller T, Dimopoulos Ma: Natural history of osteonecrosis of the jaw in patients with multiple myeloma. J Clin Oncol 26: 5904–5909, 2008

Badros A, Weikel D, Salama A, Goloubeva O, Schneider A, Rapoport A, Fenton R, Gahres N, Sausville E, Ord R, Meiller T: Osteonecrosis of the jaw in multiple myeloma patients: clinical features and risk factors. J Clin Oncol 24: 945–952, 2006

Baim S, Miller PD: Assessing the clinical utility of serum CTX in postmenopausal osteoporosis and its use in predicting risk of osteonecrosis of the jaw. J Bone Miner Res 24: 561–574, 2009

Bamias A, Kastritis E, Bamia C, Moulopoulos LA, Melakopoulos I, Bozas G, Koutsoukou V, Gika D, Anagnostopoulos A, Papadimitriou C, Terpos E, Dimopoulos MA: Osteonecrosis of the jaw in cancer after treatment with bisphosphonates: incidence and risk factors. J Clin Oncol 23: 8580–8587, 2005

Berenson JR, Hillner BE, Kyle RA, Anderson K, Lipton A, Yee GC, Biermann JS: American Society of Clinical Oncology clinical practice guidelines: the role of bisphosphonates in multiple myeloma. J Clin Oncol 20: 3719–3736, 2002

Berenson JR, Lichtenstein A, Porter L, Dimopoulos MA, Bordoni R, George S, Lipton A, Keller A, Ballester O, Kovacs MJ, Blacklock HA, Bell R, Simeone J, Reitsma DJ, Heffernan M, Seaman J, Knight RD: Efficacy of pamidronate in reducing skeletal events in patients with advanced multiple myeloma. Myeloma Aredia Study Group. N Engl J Med 334: 488–493, 1996

Black DM, Cummings SR, Karpf DB, Cauley JA, Thompson DE, Nevitt MC, Bauer DC, Genant HK, Haskell WL, Marcus R, Ott SM, Torner JC, Quandt SA, Reiss TF, Ensrud KE: Randomised trial of effect of alendronate on risk of fracture in women with existing vertebral fractures. Fracture Intervention Trial Research Group. Lancet 348: 1535–1541, 1996

Black DM, Schwartz AV, Ensrud KE, Cauley JA, Levis S, Quandt SA, Satterfield S, Wallace RB, Bauer DC, Palermo L, Wehren LE, Lombardi A, Santora AC, Cummings SR: Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. JAMA 296: 2927–2938, 2006

Bone HG, Hosking D, Devogelaer JP, Tucci JR, Emkey RD, Tonino RP, Rodriguez-Portales JA, Downs RW, Gupta J, Santora AC, Liberman UA: Ten years' experience with alendronate for osteoporosis in postmenopausal women. N Engl J Med 350: 1189–1199, 2004

Boonyapakorn T, Schirmer I, Reichart PA, Sturm I, Massenkeil G: Bisphosphonate-induced osteonecrosis of the jaws: prospective study of 80 patients with multiple myeloma and other malignancies. Oral Oncol 44: 857–869, 2008

Chavassieux PM, Arlot ME, Reda C, Wei L, Yates AJ, Meunier PJ: Histomorphometric assessment of the long-term effects of alendronate on bone quality and remodeling in patients with osteoporosis. J Clin Invest 100: 1475–1480, 1997

Corso A, Varettoni M, Zappasodi P, Klersy C, Mangiacavalli S, Pica G, Lazzarino M: A different schedule of zoledronic acid can reduce the risk of the osteonecrosis of the jaw in patients with multiple myeloma. Leukemia 21: 1545–1548, 2007

Cranney A, Tugwell P, Adachi J, Weaver B, Zytaruk N, Papaioannou A, Robinson V, Shea B, Wells G, Guyatt G: Meta-analyses of therapies for postmenopausal osteoporosis. III. Meta-analysis of risedronate for the treatment of post-menopausal osteoporosis. Endocr Rev 23: 517–523, 2002

Dimopoulos MA, Kastritis E, Anagnostopoulos A, Melakopoulos I, Gika D, Moulopoulos LA, Bamia C, Terpos E, Tsionos K, Bamias A: Osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates: evidence of increased risk after treatment with zoledronic acid. Haematologica 91: 968–971, 2006

Dimopoulos MA, Kastritis E, Bamia C, Melakopoulos I, Gika D, Roussou M, Migkou M, Eleftherakis-Papaiakovou E, Christoulas D, Terpos E, Bamias A: Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid. Ann Oncol 20: 117–120, 2009

DVO-Guideline for Prevention, Clinical assesssment and treatment of osteoporosis for women after menopause, for men after age 60. Schattauer GmbH, Germany, 2006 http://www.lutherhaus.de/osteo/leitlinien-dvo/english.php?aufklappen=RW5nbGlzY2hlIFZlcnNpb24gJ

Engroff SL, Kim DD: Treating bisphosphonate osteonecrosis of the jaws: is there a role for resection and vascularized reconstruction? J Oral Maxillofac Surg 65: 2374–2385, 2007

Farrugia MC, Summerlin DJ, Krowiak E, Huntley T, Freeman S, Borrowdale R, Tomich C: Osteonecrosis of the mandible or maxilla associated with the use of new generation bisphosphonates. Laryngoscope 116: 115–120, 2006

Hess LM, Jeter JM, Benham-Hutchins M, Alberts DS: Factors associated with osteonecrosis of the jaw among bisphosphonate users. Am J Med 121: 475–483, e3, 2008

Hong JW, Nam W, Cha IH, Chung SW, Choi HS, Kim KM, Kim KJ, Rhee Y, Lim SK: Oral bisphosphonate-related osteonecrosis of the jaw: the first report in Asia. Osteoporos Int, 2009

Khosla S, Burr D, Cauley J, Dempster DW, Ebeling PR, Felsenberg D, Gagel RF, Gilsanz V, Guise T, Koka S, Mccauley LK, Mcgowan J, Mckee MD, Mohla S, Pendrys DG, Raisz LG, Ruggiero SL, Shafer DM, Shum L, Silverman SL, Van Poznak CH, Watts N, Woo SB, Shane E: Bisphosphonate-associated osteonecrosis of the jaw: report of a task force of the American Society for Bone and Mineral Research. J Bone Miner Res 22: 1479–1491, 2007

King AE, Umland EM: Osteonecrosis of the jaw in patients receiving intravenous or oral bisphosphonates. Pharmacotherapy 28: 667–677, 2008

Kyle RA, Yee GC, Somerfield MR, Flynn PJ, Halabi S, Jagannath S, Orlowski RZ, Roodman Dg, Twilde P, Anderson K: American Society of Clinical Oncology 2007 clinical practice guideline update on the role of bisphosphonates in multiple myeloma. J Clin Oncol 25: 2464–2472, 2007

Kyrgidis A, Vahtsevanos K, Koloutsos G, Andreadis C, Boukovinas I, Teleioudis Z, Patrikidou A, Triaridis S: Bisphosphonate-related osteonecrosis of the jaws: a case–control study of risk factors in breast cancer patients. J Clin Oncol 26: 4634–4638, 2008

Lo JC, O'ryan FS, Gordon NP, Yang J, Hui RL, Martin D, Hutchinson M, Lathon PV, Sanchez G, Silver P, Chandra M, Mccloskey CA, Staffa JA, Willy M, Selby JV, Go AS: Prevalence of osteonecrosis of the jaw in patients with oral bisphosphonate exposure. J Oral Maxillofac Surg 68: 243–253, 2010

Markose G, Mackenzie FR, Currie WJ, Hislop WS: Bisphosphonate osteonecrosis: a protocol for surgical management. Br J Oral Maxillofac Surg 47: 294–297, 2009

Marx RE: Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 61: 1115–1117, 2003

Marx RE, Cillo Jr JE, Ulloa JJ: Oral bisphosphonate-induced osteonecrosis: risk factors, prediction of risk using serum CTX testing, prevention, and treatment. J Oral Maxillofac Surg 65: 2397–2410, 2007

Marx RE, Sawatari Y, Fortin M, Broumand V: Bisphosphonate-induced exposed bone (osteonecrosis/osteopetrosis) of the jaws: risk factors, recognition, prevention, and treatment. J Oral Maxillofac Surg 63: 1567–1575, 2005

McLeod NM, Davies BJ, Brennan PA: Bisphosphonate osteonecrosis of the jaws; an increasing problem for the dental practitioner. Br Dent J 203: 641–644, 2007

Migliorati CA: Bisphosphonates and oral cavity avascular bone necrosis. J Clin Oncol 21: 4253–4254, 2003

Migliorati CA, Siegel MA, Elting LS: Bisphosphonate-associated osteonecrosis: a long-term complication of bisphosphonate treatment. Lancet Oncol 7: 508–514, 2006

Mücke T, Haarmann S, Wolff KD, Hölzle F: Bisphosphonate related osteonecrosis of the jaws treated by surgical resection and immediate osseous microvascular reconstruction. J Craniomaxillofacial Surg 37: 291–297, 2009

Otto S, Hafner S, Grotz KA: The role of inferior alveolar nerve involvement in bisphosphonate-related osteonecrosis of the jaw. J Oral Maxillofac Surg 67: 589–592, 2009

Pautke C, Bauer F, Bissinger O, Tischer T, Kreutzer K, Steiner T, Weitz J, Otto S, Wolff KD, Sturzenbaum SR, Kolk A: Tetracycline bone fluorescence: a valuable marker for osteonecrosis characterization and therapy. J Oral Maxillofac Surg 68: 125–129, 2010

Pautke C, Bauer F, Tischer T, Kreutzer K, Weitz J, Kesting M, Holzle F, Kolk A, Sturzenbaum SR, Wolff KD: Fluorescence-guided bone resection in bisphosphonate-associated osteonecrosis of the jaws. J Oral Maxillofac Surg 67: 471–476, 2009

Pazianas M, Blumentals WA, Miller PD: Lack of association between oral bisphosphonates and osteonecrosis using jaw surgery as a surrogate marker. Osteoporos Int 19: 773–779, 2008

Pazianas M, Miller P, Blumentals WA, Bernal M, Kothawala P: A review of the literature on osteonecrosis of the jaw in patients with osteoporosis treated with oral bisphosphonates: prevalence, risk factors, and clinical characteristics. Clin Ther 29: 1548–1558, 2007

Piesold JU, Al-Nawas B, Grotz KA. Osteonecrosis of the jaws by long term therapy with bisphosphonates. Mund Kiefer Gesichtschir 10: 287–300, 2006

Rizzoli R, Burlet N, Cahall D, Delmas PD, Eriksen EF, Felsenberg D, Grbic J, Jontell M, Landesberg R, Laslop A, Wollenhaupt M, Papapoulos S, Sezer O, Sprafka M, Reginster JY: Osteonecrosis of the jaw and bisphosphonate treatment for osteoporosis. Bone 42: 841–847, 2008

Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B: American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws – 2009 update. J Oral Maxillofac Surg 67: 2–12, 2009

Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL: Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg 62: 527–534, 2004

Sambrook P, Cooper C: Osteoporosis. Lancet 367: 2010–2018, 2006

Silverman SL, Landesberg R: Osteonecrosis of the jaw and the role of bisphosphonates: a critical review. Am J Med 122: S33–S45, 2009

Taylor KH, Middlefell LS, Mizen KD: Osteonecrosis of the jaws induced by anti-RANK ligand therapy. Br J Oral Maxillofac Surg 2009, 2009

Walter C, Al-Nawas B, Grotz KA, Thomas C, Thuroff JW, Zinser V, Gamm H, Beck J, Wagner W: Prevalence and risk factors of bisphosphonate-associated osteonecrosis of the jaw in prostate cancer patients with advanced disease treated with zoledronate. Eur Urol 54: 1066–1072, 2008

Wang EP, Kaban LB, Strewler GJ, Raje N, Troulis MJ: Incidence of osteonecrosis of the jaw in patients with multiple myeloma and breast or prostate cancer on intravenous bisphosphonate therapy. J Oral Maxillofac Surg 65: 1328–1331, 2007

Wang J, Goodger NM, Pogrel MA: Osteonecrosis of the jaws associated with cancer chemotherapy. J Oral Maxillofac Surg 61: 1104–1107, 2003

Yarom N, Yahalom R, Shoshani Y, Hamed W, Regev E, Elad S: Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome. Osteoporos Int 18: 1363–1370, 2007