Recenti TOPIC-ISSUES dalla letteratura non-BR-ONJ

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Jaw osteonecrosis. When did it start?

BRONJ 2003

BRONJ

J Oral Maxillofac Surg
61:1115-1118, 2003

PAMIDRONATE (AREDIA) AND ZOLEDRONATE (ZOMETA) INDUCED AVASCULAR NECROSIS OF THE JAWS: A GROWING EPIDEMIC

To the Editor:—Preliminary to a manuscript submitted to a refereed scientific journal, this preliminary communication is being issued by the Division of Oral and Maxillofacial Surgery at the University of Miami School of Medicine. It identifies 36 cases of painful bone exposure in the mandible, maxilla, or both, that were unresponsive to surgical or medical treatments. All patients were receiving pamidronate (Aredia; Novartis Pharmaceuticals, East Hanover, NJ) or zoledronate (Zometa; Novartis Pharmaceuticals) therapy. It represents a heretofore unrecognized and unreported serious adverse affect; caution should be used when prescribing these drugs.

Of the 36 patients, 24 had received pamidronate (Aredia) at the prescribed dose of 90 mg intravenously (IV) monthly, 6 had received pamidronate (Aredia) at the same dose in the past but were receiving zoledronate (Zometa) 4 mg IV monthly at the time of presentation and 6 received only zoledronate (Zometa) 4 mg IV monthly. Eighteen patients

down regulation of matrix metlalloproteinases.[5] Their resultant reduction in osteoclastic activity reduces bone resorption and thus supports their published indications, which includes reducing the hypercalcemia in some malignancies and reducing osteolysis in bone metastases and in some cases of Paget's disease. However, normal osteoclasis is vital to bone turnover and bone viability. Osteocytes develop from osteoblasts, which have secreted hydroxyapatite crystals into a collagen matrix known as mineralized bone, which then encases the osteocyte. The osteocyte is a terminal cell with a life span of about 150 days.[6] As the osteocyte lives out its normal life span it no longer can maintain its mineral matrix which surrounds it and microfractures develop. Normal osteoclasis resorbs nonvital bone and releases cytokines such as bone morphogenetic protein (BMP) and insulin-like growth factors 1 and 2 (ILG_1 and ILG_2), which normally induce mesenchymal stem cells and the premitotic osteoblast to differentiate into active bone forming osteoblasts.[7] Interruption of this homeostatic cycle by overly effective inhibition of bone resorption results in the accumulation of nonvital osteocytes and micro fractures of old mineral matrix.

Bisphosphonates-related Osteonecrosis of the Jaw

Bisphosphonates

Drug name[1]	Trade name(s)	Indication
alendronic acid	Binosto® Fosamax® Fosavance®	osteoporosis
risedronate sodium	Actonel® Actonel Combi®	osteoporosis Paget's Disease
zoledronic acid	Aclasta® Zometa®	osteoporosis Paget's Disease treatment of cancer
ibandronic acid	Bondronat® Bonviva® Iasibon® Quodixor®	osteoporosis treatment of cancer
pamidronate disodium	Aredia®	Paget's Disease bone pain treatment of cancer
sodium clodronate	Bonefos® Clasteon® Loron®	bone pain treatment of cancer

[1]The three most commonly prescribed drugs are listed first

MRONJ 2014

Medication-related Osteonecrosis of the Jaw

MRONJ _ definition

Medication-related osteonecrosis of the jaw (MRONJ) is a rare side effect of anti-resorptive and anti-angiogenic drugs. It is defined as exposed bone, or bone that can be probed through an intraoral or extraoral fistula, in the maxillofacial region that has persisted for more than eight weeks in patients with a history of treatment with anti-resorptive or anti-angiogenic drugs, and where there has been no history of radiation therapy to the jaw or no obvious metastatic disease to the jaws.[1]

1 Ruggiero SL, Dodson TB, Fantasia J, et al. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw - 2014 update. *Journal of Oral and Maxillofacial Surgery*. 2014;72(10):1938-1956.

MRONJ (medication?)

2.2 What Are Anti-resorptive Drugs and How Do They Work?

Bone is constantly being remodelled by the action of osteoblasts, which create bone tissue, and osteoclasts, which break down (resorb) bone tissue. Anti-resorptive drugs inhibit osteoclast differentiation and function, leading to decreased bone resorption and remodelling. The jaw is known to have an increased remodelling rate compared to other skeletal sites and therefore the viability of bone in this region may be adversely affected by the action of these drugs.

There are two main types of anti-resorptive drugs that have been associated with osteonecrosis of the jaw, the bisphosphonates and denosumab. These are used in the management of osteoporosis and other non-malignant and malignant conditions. Anti-resorptive drugs can have a significantly positive effect on the quality of life of patients by reducing or delaying onset of disease or treatment complications, such as bone fractures and bone pain.

MRONJ (medication?)

2.3 What Are Anti-angiogenic Drugs and How Do They Work?

Anti-angiogenic drugs target the processes by which new blood vessels are formed and are used in cancer treatment to restrict tumour vascularisation.

Not all anti-angiogenic drugs are currently implicated in MRONJ. However, the vascular endothelial growth factor (VEGF) inhibitors bevacizumab and aflibercept and the receptor tyrosine kinase (RTK) inhibitor sunitinib have been associated with osteonecrosis of the jaw and the Medicines and Healthcare products Regulatory Agency (MHRA) has issued Drug Safety Updates identifying MRONJ as a possible side effect of these drugs.[20,21]

Anti-angiogenic drugs can be used in combination with the bisphosphonates in the management of cancer and there is some evidence that this results in a greater MRONJ risk.[6] This may also be true where anti-angiogenic drugs are used in patients with a previous history of bisphosphonate use.

The use of anti-angiogenic drugs in cancer is an expanding field and it is likely that any future medications with these modes of action may also have an associated risk of MRONJ.

RANKL Inhibitors

Drug name	Trade name(s)	Indication
denosumab	Prolia® Xgeva®	osteoporosis treatment of cancer

Anti-angiogenic Drugs

Drug name	Trade name(s)	Indication
bevacizumab	Avastin®	treatment of cancer
sunitinib	Sutent®	treatment of cancer
aflibercept	Zaltrap®	treatment of cancer

2014→2018

1. LITERATURE REVIEW (non-BR-ONJ)

J Craniomaxillofac Surg. 2017 Apr;45(4):570-578. doi: 10.1016/j.jcms.2017.01.013. Epub 2017 Jan 25.

Clinical course and therapeutic outcomes of operatively and non-operatively managed patients with denosumab-related osteonecrosis of the jaw (DRONJ).

Hoefert S[1], Yuan A[2], Munz A[2], Grimm M[2], Elayouti A[3], Reinert S[2].

Author information

Abstract

PURPOSE: Details regarding risk factors, onset, and outcomes for denosumab-related osteonecrosis (DRONJ) are sparse. This study examines the clinical characteristics and operative and non-operative therapeutic outcomes in patients with DRONJ not previously exposed to other antiresorptives.

METHODS: A retrospective medical record review was conducted, and data were collected, including clinical findings, management, healing outcomes, and radiologic, histologic, and micro-computed tomography (CT) analyses.

RESULTS: Seventeen patients were treated with denosumab, with 14.1 ± 8.3 doses before DRONJ onset. The majority of lesions were observed at sites of dental prostheses (41%) and dental extractions (35%). Sixteen patients were managed non-operatively (10/16) or operatively (6/16) with either major (5/6) or minor surgery (1/6) and included in the follow-up analysis. Complete healing was significant in patients treated with major surgery (80%) compared to the non-operative group (20%; $p < 0.035$). Denosumab was discontinued in 60% of non-operative patients and major surgery patients with no effect on healing. Histologic findings of 4 patients analyzed exhibited a decreased number of osteocyte lacunae, and micro-CT of 3 patients scanned revealed trabecular thickening.

CONCLUSION: DRONJ lesions occurred mostly at sites of prostheses sores after a mean of 14 doses of denosumab. Major surgery demonstrated more complete healing than non-operative management, and denosumab cessation did not improve healing outcomes.

KEYWORDS: Bisphosphonates; Denosumab; Medication-related osteonecrosis of the jaw; Osteonecrosis

PMID: 28238559 DOI: 10.1016/j.jcms.2017.01.013

[Indexed for MEDLINE]

Format: Abstract Send to

J Bone Miner Metab. 2017 Jan;35(1):6-19. doi: 10.1007/s00774-016-0810-7. Epub 2016 Dec 29.

Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw.

Japanese Allied Committee on Osteonecrosis of the Jaw, Yoneda T[1,2], Hagino H[3,4], Sugimoto T[5,4], Ohta H[6,7], Takahashi S[8,4], Soen S[9,7], Taguchi A[10,11], Nagata T[12,13], Urade M[14,15], Shibahara T[16,15], Toyosawa S[17,18].

Author information

Erratum in

Erratum to: Antiresorptive agent-related osteonecrosis of the jaw: Position Paper 2017 of the Japanese Allied Committee on Osteonecrosis of the Jaw. [J Bone Miner Metab. 2017]

Abstract

Antiresorptive agent-related osteonecrosis of the jaw (ARONJ) is an intractable, though rare, complication in cancer patients with bone metastases and patients with osteoporosis who are treated with antiresorptive agents, including bisphosphonates and denosumab. Despite the more than 10 years that have passed since the first cases of bisphosphonate-related osteonecrosis of the jaw (BRONJ) were reported, our understanding of the epidemiology and pathophysiology of ARONJ remains limited, and data supported by evidence-based medicine are still sparse. However, the diagnosis and staging of ARONJ, identification of risk factors, and development of preventive and therapeutic approaches have advanced significantly over the past decade. The Position Paper 2017 is an updated version of the Position Paper 2010 of the Japanese Allied Committee on Osteonecrosis of the Jaw, which now comprises six Japanese academic societies. The Position Paper 2017 describes a new diagnostic definition for ARONJ, as proposed by the American Association of Oral and Maxillofacial Surgeons (AAOMS), summarizes our current understanding of the pathophysiology of ARONJ based on a literature search, and suggests methods for physicians and dentists/oral surgeons to manage the disease. In addition, the appropriateness of discontinuing antiresorptive medications (drug holiday) before, during, and after invasive dental treatments is discussed extensively. More importantly, the manuscript also proposes, for the first time, the importance of interactive communication and cooperation between physicians and dentists/oral surgeons for the successful treatment of ARONJ. The Position Paper 2017 is intended to serve as a guide for improving the management of ARONJ patients in Japan.

KEYWORDS: Bisphosphonates; Denosumab; Drug holidays; Oral bacterial infection; Osteonecrosis of the jaw; Team therapeutic approaches

PMID: 28035494 DOI: 10.1007/s00774-016-0810-7

[Indexed for MEDLINE]

Format: Abstract Send to

J Oral Maxillofac Surg. 2010 May;68(5):959-63. doi: 10.1016/j.joms.2009.10.010. Epub 2010 Feb 10.

Osteonecrosis of the jaw in a patient on Denosumab.

Aghaloo TL[1], Felsenfeld AL, Tetradis S.

Author information

PMID: 20149510 PMCID: PMC2880179 DOI: 10.1016/j.joms.2009.10.010

[Indexed for MEDLINE] Free PMC Article

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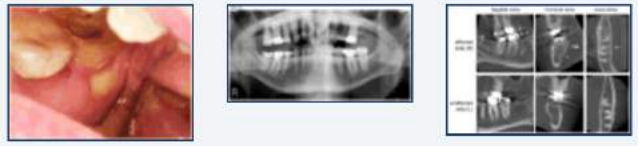

Publication types, MeSH terms, Substances, Grant support

LinkOut - more resources

Format: Abstract Send to

Breast Cancer Res Treat. 2010 Jul;122(1):181-8. doi: 10.1007/s10549-010-0866-3. Epub 2010 Apr 2.

Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer.

Guarneri V[1], Miles D, Robert N, Diéras V, Glaspy J, Smith I, Thomssen C, Biganzoli L, Taran T, Conte P.

Author information

Abstract

Long-term bisphosphonate therapy is associated with increased risk of osteonecrosis of the jaw (ONJ). In a retrospective analysis, a 16% ONJ incidence was reported in patients receiving bisphosphonates with anti-angiogenic therapy (bevacizumab or sunitinib) for bone metastases from breast, colon, or renal cell cancers. To assess ONJ incidence with bevacizumab, we analysed data from 3,560 patients receiving bevacizumab-containing therapy for locally recurrent or metastatic breast cancer (LR/MBC) in two double-blind, randomised trials (AVADO and RIBBON-1) and a large, non-randomised safety study (ATHENA). The overall incidence of ONJ with bevacizumab was 0.3% in the blinded phase of the two randomised trials and 0.4% in the single-arm study. There was a trend towards increased ONJ incidence in patients who received bisphosphonate therapy versus those with no bisphosphonate exposure (0.9 vs. 0.2%, respectively, in the pooled analysis of the randomised trials; 2.4 vs. 0%, respectively, in ATHENA). In conclusion, this is the largest analysis of ONJ in patients receiving bevacizumab for LR/MBC. The 0.3-0.4% incidence is considerably lower than previously suggested with anti-angiogenic therapy in a small retrospective analysis. The risk of ONJ appeared to be increased in patients exposed to bisphosphonates, a pattern consistent with observations before the introduction of anti-angiogenic therapy to breast cancer management. The 0.9-2.4% incidence seen in bisphosphonate-exposed patients receiving bevacizumab is within the 1-6% range reported for bisphosphonates alone. Good oral hygiene, dental examination, and avoidance of invasive dental procedures remain important in patients receiving bisphosphonates, irrespective of bevacizumab administration.

Comment in

Osteonecrosis of the jaw and bevacizumab therapy. [Breast Cancer Res Treat. 2010]

PMID: 20361252 DOI: 10.1007/s10549-010-0866-3

[Indexed for MEDLINE]

Publication type, MeSH terms, Substances

Oral Surg Oral Med Oral Pathol Oral Radiol Endod. 2010 Oct;110(4):463-9. doi: 10.1016/j.tripleo.2010.04.049. Epub 2010 Aug 9.

Sunitinib may raise the risk of bisphosphonate-related osteonecrosis of the jaw: presentation of three cases.

Hoefert S[1], Eufinger H.

Author information

Abstract

OBJECTIVE: Bisphosphonate-related osteonecrosis of the jaw (BRONJ) is a serious side effect of bisphosphonate (BP) medication. Tooth extractions are the most frequent causes for BRONJ. In some cases BRONJ is observed spontaneously, with some anatomic sites carrying a higher risk. Sunitinib, a tyrosine kinase inhibitor, is established in renal cell carcinoma and is known to lead to oral mucositis as a side effect, which in BP patients may additionally raise the risk of BRONJ.

STUDY DESIGN: We present 3 patients with renal cell carcinoma under BP medication who developed BRONJ during and after sunitinib medication.

RESULTS: In 2 patients, BRONJ was linked to the occurrence of mucositis after sunitinib intake. The third patient showed relapse of completely healed BRONJ lesions shortly after resumption of a sunitinib therapy.

CONCLUSIONS: Oral mucositis during chemotherapy may raise the risk of BRONJ in cancer patients with BP medication. Especially in renal cell carcinoma patients under sunitinib therapy and intravenous BP medication, oral mucositis should be observed closely because it could be a risk factor for BRONJ.

PMID: 20692189 DOI: 10.1016/j.tripleo.2010.04.049

[Indexed for MEDLINE]

2014-2018 (21st of April)

- *Denosumab*
- *Bevacizumab*
- *Sunitinib*
- *Aflibercept*
- *Axitinib*
- *Everolimus*
- *Methotrexate*
- *Imatinib*
- *Raloxifene*
- *Infliximab*
- *Erlotinib*
- *Dasatinib*
- *Rituximab*
- *Imatinib*
- *Adalimumab*
- *Regorafenib*
- *Sorafenib*
- *Ipilimumab*
- *Cabozantinib*
- *Romosozumab*

2014-2018

- *Denosumab*
- ***Bevacizumab → a.a.g.***
- ***Sunitinib → i.RTK***
- ***Aflibercept → a.a.g.***
- ***Axitinib → i.RTK***
- ***Everolimus → i.mTOR***
- ***Methotrexate → i.s.***
- ***Imatinib → i.RTK***
- ***Raloxifene → SERMs***
- ***Infliximab → a.TNF***
- ***Erlotinib → i.RTK***
- ***Dasatinib → i.RTK***
- ***Rituximab → a.CD20***
- ***Imatinib → i.RTK***
- ***Adalimumab → a.TNF***
- ***Regorafenib → i.RTK***
- ***Sorafenib → a.FAK***
- ***Ipilimumab → anti-CTLA-4***
- ***Cabozantinib → i.RTK***
- ***Romosozumab → s.m.a.***
- ***Regorafenib → a.a.g.***

MRONJ _ incidence

MRONJ Incidence in Cancer Patients

MRONJ has been observed in patients being treated with anti-resorptive or anti-angiogenic drugs for management of solid tumour cancers (e.g. breast cancer, prostate cancer) and multiple myeloma and other cancers of the blood. Estimates of incidence and prevalence vary due to the rare nature of MRONJ. In these cancer patients, the MRONJ risk ranges from 0 to 12% (0-1200 cases per 10,000)[2-5] compared to a risk of 0 to 0.02% (0-2 cases of ONJ per 10,000) in cancer patients exposed to placebo in clinical trials.[1] However, it should be noted that estimates towards the higher end of this range tended to come from studies with small sample sizes which can overestimate the risk of low frequency events. When only considering data from studies with >500 patients, the risk of MRONJ in cancer patients approximates 1% (ranging from 0 to 2.3%).‡ This agrees with an estimate of MRONJ risk based on studies with Level 1 evidence (systematic reviews or RCTs).[1] However, it should be noted that incidence may vary depending on cancer type and treatment regime, with patients with prostate cancer or multiple myeloma thought to be at increased risk. There are fewer data available to estimate the risk of MRONJ in cancer patients treated with anti-angiogenic drugs. However, one study reports a risk of 0.2% (20 cases per 10,000) in cancer patients treated with bevacizumab.[6] It also appears the risk is increased when anti-angiogenics are used in conjunction with anti-resorptive drugs (both given simultaneously) or are given to those with a history of bisphosphonate use.[1]

MRONJ _ incidence

Estimated incidence of MRONJ in cancer patients treated with anti-resorptive or anti-angiogenic drugs	**1%** (1 case per 100)
Estimated incidence of MRONJ in osteoporosis patients treated with anti-resorptive drugs	**0.01-0.1%** (1-10 cases per 10,000)

non-BR-ONJ _ incidence worldwide

ORIGINAL ARTICLE

JBMR®

Osteonecrosis of the Jaw in the United States Food and Drug Administration's Adverse Event Reporting System (FAERS)

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ABSTRACT

Osteonecrosis of the jaw (ONJ) is a serious adverse drug event that was initially reported with intravenous bisphosphonates (BPs) and more recently with other classes of drugs such as receptor activator of NF-κB ligand (RANKL) inhibitor, antiangiogenic agents, and mammalian target of rapamycin (m-TOR) inhibitors. The purpose of this study is to analyze the ONJ cases and the associated drugs in the US Food and Drug Administration's adverse event reporting system (FAERS). The FAERS database was queried for the adverse drug events reported from the first quarter of 2010 to the first quarter of 2014. The reporting odds ratios (ORs) and 95% confidence intervals (CIs) were calculated for each queried drug. A total of 17,119 unique ONJ cases were identified. In the overall analysis, the drugs with the highest reporting ORs were BPs: pamidronate (OR = 498.9), zoledronate (OR = 171.7), and alendronate (OR = 63.6), whereas denosumab had lower ORs than all the BPs except for etidronate. The antiangiogenic and m-TOR inhibitors had the lowest ORs. In cancer patients who were treated for prevention of skeletal-related events (SREs), the reporting ORs for zoledronate and denosumab were 125.2 and 4.9, respectively. In patients with osteoporosis, the ORs were 1.1 (1.0–1.18) for zoledronate and 0.63 (0.56–0.70) for denosumab, respectively. Our analysis of the FAERS database showed that the intravenous BPs were associated with the highest risk for ONJ, RANKL inhibitor was associated with risk comparable to BPs used for osteoporosis such as etidronate, and the antiangiogenic agents and m-TOR inhibitors were associated with the lowest risk for ONJ. The high risk for ONJ with zoledronate and denosumab was mainly observed in those who were treated for prevention of SREs, whereas there was limited evidence for such risk in those who were treated for osteoporosis.

KEY WORDS: OSTEONECROSIS OF THE JAW; FAERS; BISPHOSPHONATES; RANKL INHIBITORS; ANTIANGIOGENIC AGENTS

Table 1. Demographics of the Osteonecrosis of the Jaw Cases Reported in FAERS Between the First Quarter of 2010 and the First Quarter of 2014

	All ONJ cases ($n = 17,119$)	SRE ($n = 6930$)	Osteoporosis ($n = 4760$)
Age (years) (mean ± SD)	62.2 ± 12.1	66.5 ± 15.4	63.0 ± 11.8
Male (%)	30.3%	41.2%	10.0%
Country reported			
United States	69.7%	55.7%	84.2%
Japan	6.8%	13.0%	1.6%
Germany	5.6%	6.5%	3.0%
Italy	3.6%	7.1%	0.5%
France	1.5%	2.3%	0.9%
United Kingdom	1.5%	1.7%	0.6%
Medications			
Bisphosphonates			
Zoledronate	11490 (67.1%)	6200 (89.5%)	809 (17.0%)
Alendronate	7307 (42.7%)	350 (5.1%)	4020 (84.5%)
Pamidronate	5251 (30.7%)	2485 (35.9%)	330 (6.9%)
Risedronate	827 (4.8%)	93 (1.3%)	566 (11.9%)
Ibandronate	786 (4.6%)	60 (0.9%)	600 (12.6%)
Clodronate	33 (0.2%)	19 (0.3%)	9 (0.2%)
Etidronate	28 (0.2%)	1 (0.01%)	23 (0.5%)
RANKL inhibitor			
Denosumab	1184 (6.9%)	441 (6.4%)	376 (7.9%)
Antiangiogenic agents			
Bevacizumab	703 (4.1%)	395 (5.7%)	22 (0.5%)
Sunitinib	418 (2.4%)	292 (4.2%)	na
Sorafenib	90 (0.5%)	41 (0.6%)	na
Pazopanib	10 (0.1%)	9 (0.1%)	na
Axitinib	9 (0.1%)	8 (0.1%)	na
m-TOR inhibitor			
Everolimus	84 (0.5%)	71 (1%)	3 (0.1%)
Temsirolimus	28 (0.2%)	18 (0.3%)	1 (0.02%)

ONJ = osteonecrosis of the jaw; SRE = skeletal related events.
Values presented are *n* (%) unless stated otherwise.
Note that not all ONJ cases had clear indications for use of medications.

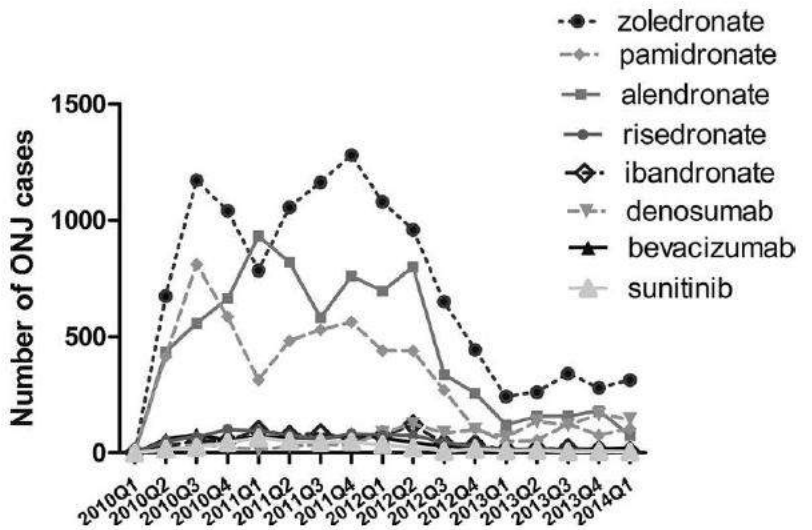

Fig. 2. The numbers of ONJ cases for each drug by quarter from the first quarter of 2010 through the first quarter of 2014.

non-BR-ONJ _ incidence

- 1 case per 666 cancer patients treated
- 1 case per 10.000 osteoporotic patients

Lancet Diabetes Endocrinol. 2017 Jul;5(7):513-523. doi: 10.1016/S2213-8587(17)30138-9. Epub 2017 May 22.

10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension.

Bone HG[1], Wagman RB[2], Brandi ML[3], Brown JP[4], Chapurlat R[5], Cummings SR[6], Czerwiński E[7], Fahrleitner-Pammer A[8], Kendler DL[9], Lippuner K[10], Reginster JY[11], Roux C[12], Malouf J[13], Bradley MN[2], Daizadeh NS[2], Wang A[2], Dakin P[2], Pannacciulli N[2], Dempster DW[14], Papapoulos S[15].

Author information

Abstract

BACKGROUND: Long-term safety and efficacy of osteoporosis treatment are important because of the chronic nature of the disease. We aimed to assess the long-term safety and efficacy of denosumab, which is widely used for the treatment of postmenopausal women with osteoporosis.

METHODS: In the multicentre, randomised, double-blind, placebo-controlled, phase 3 FREEDOM trial, postmenopausal women aged 60-90 years with osteoporosis were enrolled in 214 centres in North America, Europe, Latin America, and Australasia and were randomly assigned (1:1) to receive 60 mg subcutaneous denosumab or placebo every 6 months for 3 years. All participants who completed the FREEDOM trial without discontinuing treatment or missing more than one dose of investigational product were eligible to enrol in the open-label, 7-year extension, in which all participants received denosumab. The data represent up to 10 years of denosumab exposure for women who received 3 years of denosumab in FREEDOM and continued in the extension (long-term group), and up to 7 years for women who received 3 years of placebo and transitioned to denosumab in the extension (crossover group). The primary outcome was safety monitoring, comprising assessments of adverse event incidence and serious adverse event incidence, changes in safety laboratory analytes (ie, serum chemistry and haematology), and participant incidence of denosumab antibody formation. Secondary outcomes included new vertebral, hip, and non-vertebral fractures as well as bone mineral density (BMD) at the lumbar spine, total hip, femoral neck, and one-third radius. Analyses were done according to the randomised FREEDOM treatment assignments. All participants who received at least one dose of investigational product in FREEDOM or the extension were included in the combined safety analyses. All participants who enrolled in the extension with observed data were included in the efficacy analyses. The FREEDOM trial (NCT00089791) and its extension (NCT00523341) are both registered with ClinicalTrials.gov.

FINDINGS: Between Aug 3, 2004, and June 1, 2005, 7808 women were enrolled in the FREEDOM study. 5928 (76%) women were eligible for enrolment in the extension, and of these, 4550 (77%) were enrolled (2343 long-term, 2207 crossover) between Aug 7, 2007, and June 20, 2008. 2626 women (1343 long-term; 1283 crossover) completed the extension. The yearly exposure-adjusted participant incidence of adverse events for all individuals receiving denosumab decreased from 165·3 to 95·9 per 100 participant-years over the course of 10 years. Serious adverse event rates were generally stable over time, varying between 11·5 and 14·4 per 100 participant-years. One atypical femoral fracture occurred in each group during the extension. Seven cases of osteonecrosis of the jaw were reported in the long-term group and six cases in the crossover group. The yearly incidence of new vertebral fractures (ranging from 0·90% to 1·86%) and non-vertebral fractures (ranging from 0·84% to 2·55%) remained low during the extension, similar to rates observed in the denosumab group during the first three years of the FREEDOM study, and lower than rates projected for a virtual long-term placebo cohort. In the long-term group, BMD increased from FREEDOM baseline by 21·7% at the lumbar spine, 9·2% at total hip, 9·0% at femoral neck, and 2·7% at the one-third radius. In the crossover group, BMD increased from extension baseline by 16·5% at the lumbar spine, 7·4% at total hip, 7·1% at femoral neck, and 2·3% at one-third radius.

Table 2. Drugs Associated With ONJ and the Reporting Odds Ratios in FAERS

Drug	Drug class	OR	95% Confidence interval	*p* Value
Pamidronate	BP	498.9	(475.2–523.8)	<0.0001
Zoledronate	BP	171.7	(166.1–177.6)	<0.0001
Alendronate	BP	63.6	(61.6–65.7)	<0.0001
Clodronate	BP	33.0	(22.8–47.7)	<0.0001
Risedronate	BP	16.6	(15.4–17.8)	<0.0001
Ibandronate	BP	16.3	(15.1–17.6)	<0.0001
Denosumab	RANKL inhibitor	13.8	(13.0–14.7)	<0.0001
Etidronate	BP	12.3	(8.4–18.0)	<0.0001
Sunitinib	Antiangiogenic	4.6	(4.2–5.1)	<0.0001
Bevacizumab	Antiangiogenic	4.5	(4.2–4.9)	<0.0001
Temsirolimus	m-TOR inhibitor	3.1	(2.2–4.6)	<0.0001
Sorafenib	Antiangiogenic	1.5	(1.2–1.9)	<0.0001
Everolimus	m-TOR inhibitor	1.4	(1.2–1.8)	0.0008
Pazopanib	Antiangiogenic	1.3	(0.7–2.5)	0.38
Axitinib	Antiangiogenic	0.8	(0.4–1.5)	0.49

OR = reporting odds ratio; BP = bisphosphonates; RANKL = human monoclonal antibody to the receptor activator of nuclear factor-κB ligand; m-TOR inhibitor = mammalian target of rapamycin inhibitor.

The estimated reporting ORs for each of the individual drugs associated with ONJ are summarized in Table 2. The drugs with the highest ORs were BPs, particularly pamidronate (OR = 498.9, 95% CI: 475.2–523.8) and zoledronate (OR = 171.7, 95% CI: 166.1–177.6). The RANKL inhibitor denosumab (OR = 13.8, 95% CI: 13.0–14.7) had a slightly lower OR compared with ibandronate (16.3) and risedronate (16.6). The antiangiogenic agents had modest ORs: 4.6 for sunitinib (95% CI: 4.2–5.1) and 4.5 for bevacizumab (95% CI: 4.2–4.9), respectively. The only other antiangiogenic agent that was significantly associated with higher risk of ONJ was sorafenib (OR = 1.5, 95% CI: 1.2–1.9, $p < 0.0001$). There was no evidence that the other two antiangiogenic agents, pazopanib and axitinib, were statistically associated with ONJ. Both m-TOR inhibitors were significantly associated with ONJ with OR = 3.1 (95% CI: 2.2–4.6, $p < 0.0001$) and OR = 1.4 (95% CI: 1.2–1.8, $p = 0.0008$) for temsirolimus and everolimus, respectively.

Because zoledronate and denosumab could be used for the prevention of SREs and in patients with osteoporosis, we separately calculated the reporting ORs of these two drugs in these two settings. In cancer patients who were treated for prevention of SREs, the ORs for zoledronate and denosumab were 125.2 (95% CI: 115.7–135.8, $p < 0.0001$) and 4.9 (95% CI: 4.4–5.4, $p < 0.0001$), respectively. In patients with osteoporosis, the ORs were 1.1 (95% CI: 1.0–1.18, $p = 0.029$) for zoledronate and 0.63 (95% CI: 0.56–0.70, $p < 0.0001$) for denosumab, respectively.

Table 2. Drugs Associated With ONJ and the Reporting Odds Ratios in FAERS

Drug	Drug class	OR	95% Confidence interval	*p* Value
Pamidronate	BP	498.9	(475.2–523.8)	<0.0001
Zoledronate	BP	171.7	(166.1–177.6)	<0.0001
Alendronate	BP	63.6	(61.6–65.7)	<0.0001
Clodronate	BP	33.0	(22.8–47.7)	<0.0001
Risedronate	BP	16.6	(15.4–17.8)	<0.0001
Ibandronate	BP	16.3	(15.1–17.6)	<0.0001
Denosumab	RANKL inhibitor	13.8	(13.0–14.7)	<0.0001
Etidronate	BP	12.3	(8.4–18.0)	<0.0001
Sunitinib	Antiangiogenic	4.6	(4.2–5.1)	<0.0001
Bevacizumab	Antiangiogenic	4.5	(4.2–4.9)	<0.0001
Temsirolimus	m-TOR inhibitor	3.1	(2.2–4.6)	<0.0001
Sorafenib	Antiangiogenic	1.5	(1.2–1.9)	<0.0001
Everolimus	m-TOR inhibitor	1.4	(1.2–1.8)	0.0008
Pazopanib	Antiangiogenic	1.3	(0.7–2.5)	0.38
Axitinib	Antiangiogenic	0.8	(0.4–1.5)	0.49

OR = reporting odds ratio; BP = bisphosphonates; RANKL = human monoclonal antibody to the receptor activator of nuclear factor-κB ligand; m-TOR inhibitor = mammalian target of rapamycin inhibitor.

The estimated reporting ORs for each of the individual drugs associated with ONJ are summarized in Table 2. The drugs with the highest ORs were BPs, particularly pamidronate (OR = 498.9, 95% CI: 475.2–523.8) and zoledronate (OR = 171.7, 95% CI: 166.1–177.6). The RANKL inhibitor denosumab (OR = 13.8, 95% CI: 13.0–14.7) had a slightly lower OR compared with ibandronate (16.3) and risedronate (16.6). The antiangiogenic agents had modest ORs: 4.6 for sunitinib (95% CI: 4.2–5.1) and 4.5 for bevacizumab (95% CI: 4.2–4.9), respectively. The only other antiangiogenic agent that was significantly associated with higher risk of ONJ was sorafenib (OR = 1.5, 95% CI: 1.2–1.9, $p < 0.0001$). There was no evidence that the other two antiangiogenic agents, pazopanib and axitinib, were statistically associated with ONJ. Both m-TOR inhibitors were significantly associated with ONJ with OR = 3.1 (95% CI: 2.2–4.6, $p < 0.0001$) and OR = 1.4 (95% CI: 1.2–1.8, $p = 0.0008$) for temsirolimus and everolimus, respectively.

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non-BR-ONJ _ incidence Piedmont

Patients and methods. We asked for new ONJ cases observed between January 2009 and March 2016. We identified cases after cross-checking reports from medical oncology, haematology, and oral care centers to avoid double count.

Results. We received partial data about 370 cancer and myeloma patients. Sex: 65% female, 35% male (**FIG.1**).

Primary disease: breast cancer 46%, myeloma 20%, prostate cancer 20%, other (lung, renal cell and other types of cancer or not specified) 13% (**FIG.2**).

The median number of new cases per year was 39 (range 30-49) in years 2009-2016; number of cases per year: median 46 (range 28-54). (**FIG.3**)

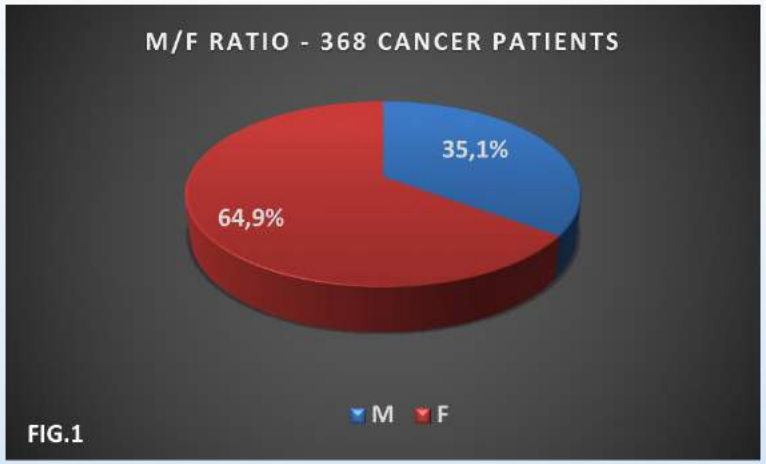
Main administered drug: zoledronate 73%, denosumab 7%, pamidronate 4%, other BPs or antiangiogenic drugs alone 1%. (**FIG.4);** 38 patients were administered with two different BFs (**FIG.5**).

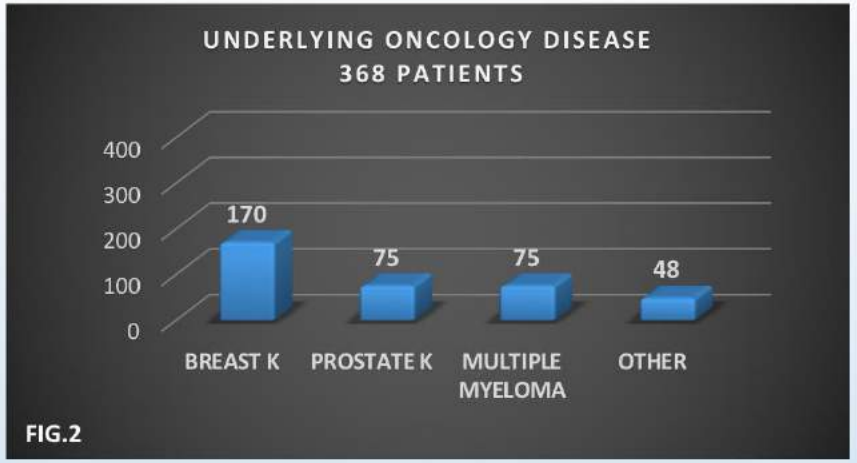
First site: mandible 65%, maxilla 35% (**FIG.6**).

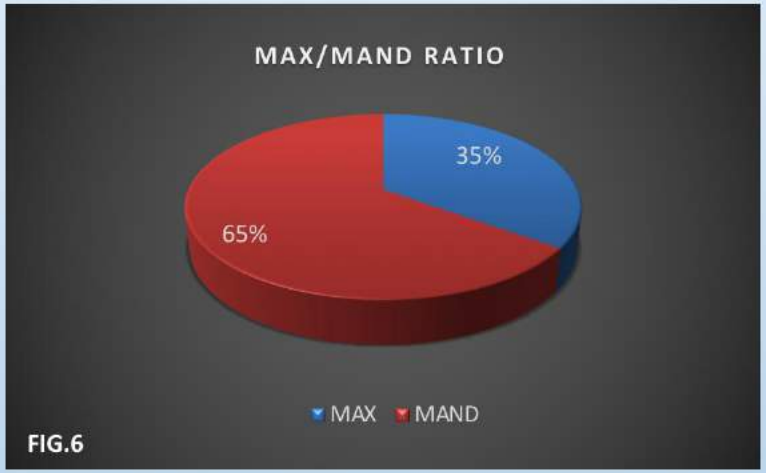
Local visits to collect complete data of all cases (duration and doses of therapy; concomitant treatments and diseases; oral health risk factors) are ongoing.

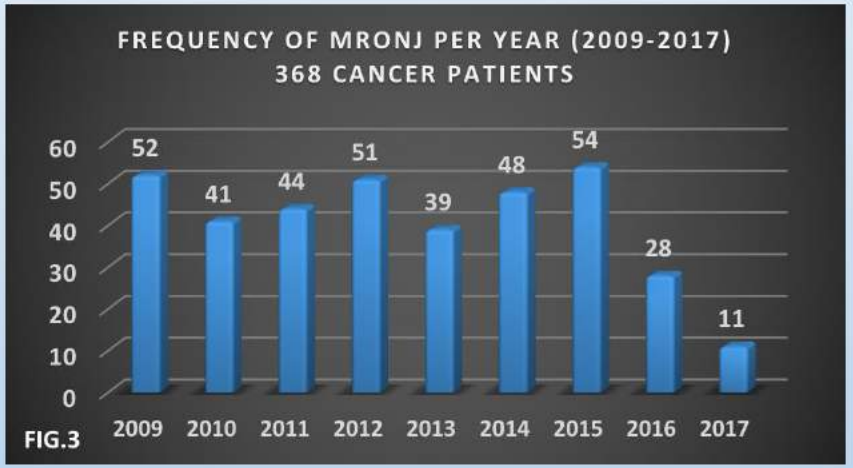
Conclusions. Preliminary data show an unexpected increase of new ONJ cases per year, in spite of measures prescribed to reduce the ONJ risk (recommended dental visit and oral care before antiresorptive treatment). Possible reasons include: introduction of denosumab treatment in bone metastatic patients; larger use of biological agents potentially inducing ONJ; longer survival of some subsets of cancer patients (eg, lung and renal cell cancer, etc);) in recent years; higher risk from antiresorptive plus antiangiogenic drugs.

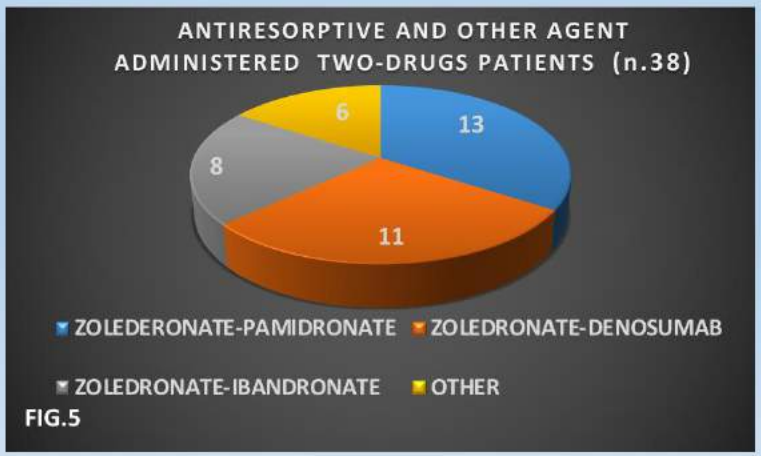
(figures clockwise)

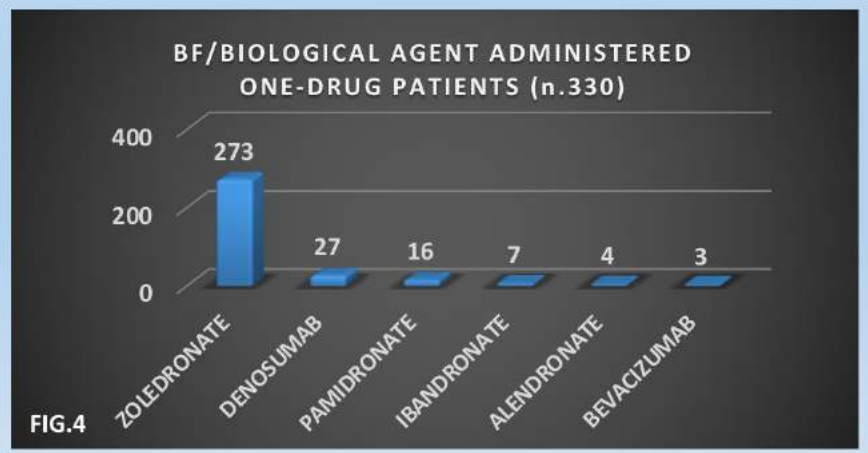












non-BR-ONJ _ difference with BRONJ?

non-BR-ONJ _ difference with BRONJ?

- No difference in comorbidities

Received: 23 May 2017 | Revised: 15 June 2017 | Accepted: 21 June 2017
DOI: 10.1111/odi.12708

REVIEW ARTICLE

WILEY ORAL DISEASES

Risk factors for medication-related osteonecrosis of the jaws: A systematic review

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The purpose of this study was to identify the patient populations at risk of medication-related osteonecrosis of the jaw (MRONJ) and determine which medical and dental comorbidities are significant risk factors for this disease. An electronic search of Embase, MEDLINE, Cochrane Central Register of Controlled Trials, WHO International Clinical Trials Registry Platform and ProQuest Dissertations and Theses Global was conducted to identify all human studies that reported risk factors for MRONJ. Only a qualitative analysis was performed due to significant heterogeneity in the collected data. The search strategy identified 2872 records, of which 219 studies were eligible for inclusion. A total of 4106 patients with MRONJ were identified, 39 different systemic diseases were implicated, and 14 medical and 11 dental risk factors were reported, although no statistical analysis of the significance of each of these factors was possible. The clinical reach of MRONJ may be wider than anticipated, and more data on the significance of each potential risk factor are needed to guide the identification and management of at-risk patients.

KEYWORDS
anti-neoplastic agents, bone density conservation agents, cancer, molecular targeted therapy, osteoporosis, preventative dentistry

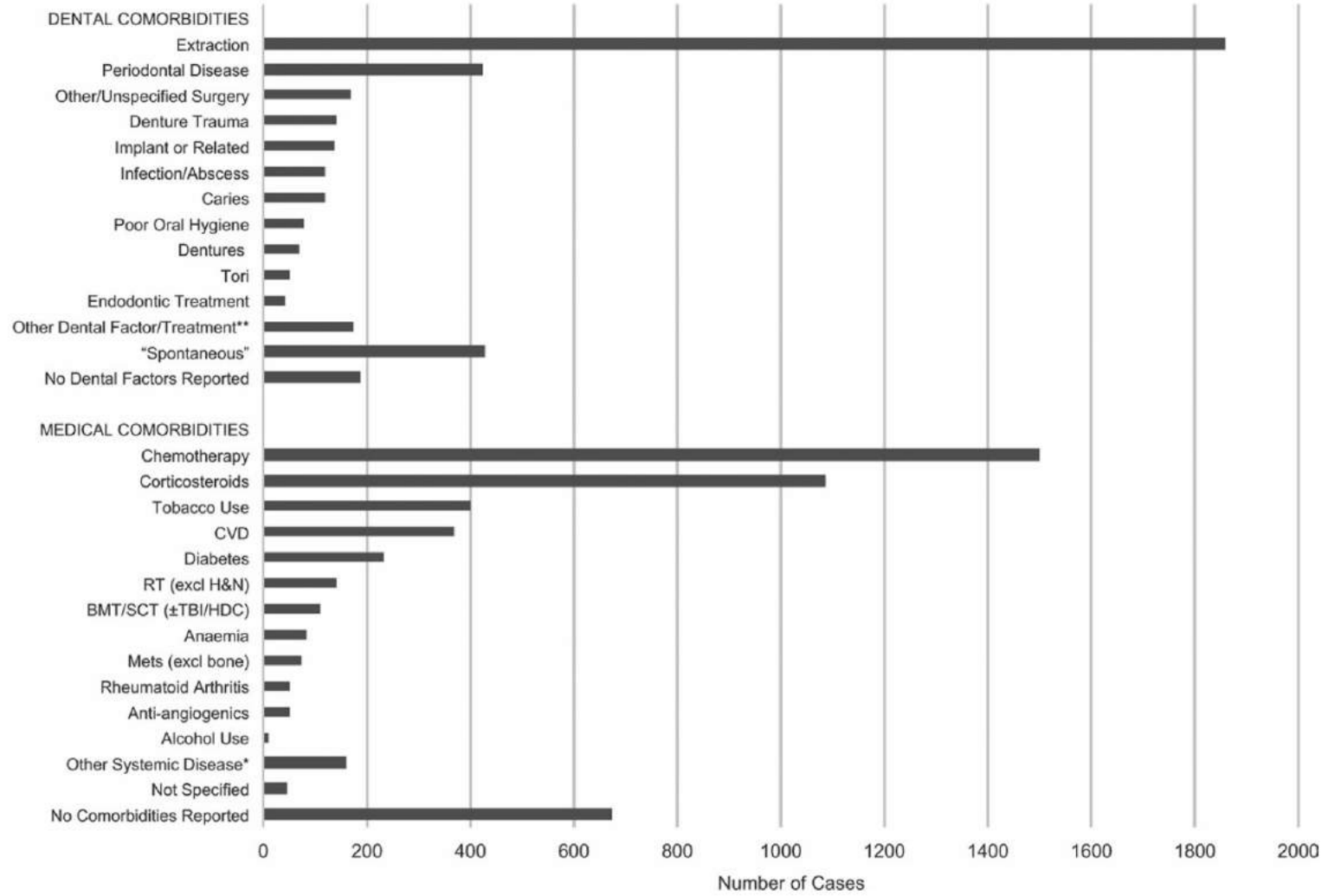


FIGURE 2 Incidence of medical and dental comorbidities reported in the included literature from a total of 4106 cases of ONJ. Data demonstrate general trends only and are not representative of relative risk due to significant inconsistencies in reported data points. *"Other Systemic Diseases" included gastro-oesophageal reflux disease, Crohn's disease, gastritis, Sjögren's syndrome, sarcoidosis, chronic obstructive pulmonary disease, kidney transplant, renal failure/insufficiency, Parkinson's disease, dementia, thrombotic event, liver disease, asthma, angina, Lupus, obesity, stomatitis, cerebral infarction, hypothyroidism, osteoarthritis and pulmonary embolism. **"Other Dental Factor/Treatment" included fixed partial denture, crown preparation, trauma from impression tray or intubation, mylohyoid ridge and knife-edge ridge. Abbreviations: Mets, metastases; RT, radiation therapy; BMT/SCT, bone marrow transplant/stem cell transplant; TBI/HDC, total body irradiation/high dose chemotherapy; CVD, cardiovascular disease

non-BR-ONJ _ difference with BRONJ?

- No clinical differences

non-BR-ONJ _ difference with BRONJ?

- No radiological differences

non-BR-ONJ _ difference with BRONJ?

Duration of Bisphosphonate Drug Therapy

The risk of MRONJ in patients being treated with bisphosphonate drugs is thought to increase as the cumulative dose of the drug increases, as a consequence of the long half-life of this drug class. This may explain the increased MRONJ risk in patients being treated with high dose bisphosphonate drugs for the management of cancer compared to those being treated with the lower dose, mostly oral drugs for the management of osteoporosis or other non-malignant diseases of the bone. However, even in this lower risk patient group, the MRONJ risk may be influenced by the length of time that a patient has been exposed to the drug, with one study finding a higher prevalence of MRONJ in patients who had taken oral bisphosphonates for more than four years compared to those who had taken the drugs for less than this time period.[12]

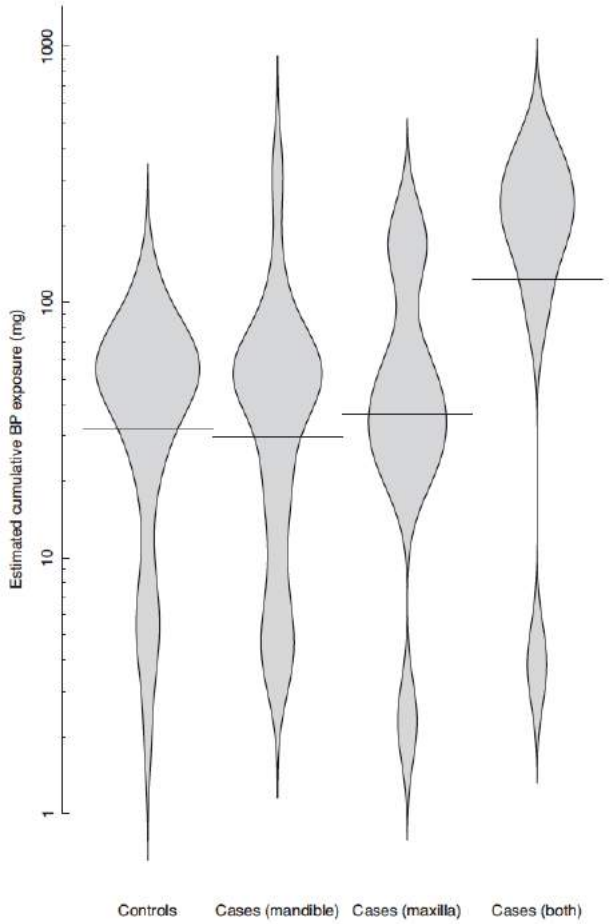


Fig. 2. Beanplots depicting the difference in CBPE between cases and controls. Cases are stratified by location of osteonecrosis (BRONJ diagnosed only in mandible, only in maxilla, or in both bones). Horizontal lines represent median of CBPE levels.

3.2. *Cumulative BP exposure and BRONJ*

Preliminary investigations of the CBPE distribution indicated that the cases were slightly more exposed than the controls. As shown in Fig. 2, the median CBPE in cases diagnosed with BRONJ in both mandible and maxilla is significantly higher than in controls (one-sided Wilcoxon rank sum test, $p = 0.002$). The overall distribution is also shifted toward the higher end of the range of exposure compared to cases diagnosed with BRONJ in either mandible or maxilla. Case/control analysis by means of logistic regression (Table S1) confirmed the positive association between cumulative BP exposure and risk of BRONJ (OR 1.015, 95% CI 1.004–1.032, $p = 0.036$).

Table 1
Study population characteristics.

	Cases							Controls			
	Gender		Age	CBPE	Location			Gender		Age	CBPE
	M	F			MN	MX	Both	M	F		
Multiple myeloma	3	5	61.50 (49–79)	71.50 (32.00–200.00)	5	1	2	2	2	59.50 (56–62)	85.00 (64.00–116.00)
Breast cancer		15	67.73 (46–81)	132.00 (20.00–368.00)*	6	5	4		16	64.69 (44–79)	51.00 (24.00–120.00)
Prostate cancer	5		73.00 (66–85)	87.20 (20.00–180.00)	3	2	0	6		65.33 (47–73)	54.67 (48.00–68.00)
Osteoporosis		7	71.14 (64–83)	5.30 (2.30–11.50)	5	1	1		7	72.14 (60–79)	5.97 (1.92–12.65)
Overall population	8	27	67.74 (46–85)	86.43 (2.30–368.00)*	19	9	7	8	25	65.76 (44–79)	46.24 (1.92–120.00)

Age and cumulative BP exposure reported as mean (range). MN, mandible; MX, maxilla.
* Significant difference ($p < 0.05$) between cases and controls (two-sided t-test).

Oral Dis. 2017 May;23(4):477-483. doi: 10.1111/odi.12632. Epub 2017 Mar 6.

Time to onset of bisphosphonate-related osteonecrosis of the jaws: a multicentre retrospective cohort study.

Fung P[1], Bedogni G[2], Bedogni A[3,4], Petrie A[1], Porter S[1], Campisi G[5], Bagan J[6], Fusco V[7], Saia G[4], Acham S[8], Musto P[9], Petrucci MT[10], Diz P[11], Colella G[12], Mignogna MD[13], Pentenero M[14], Arduino P[15], Lodi G[16], Maiorana C[17], Manfredi M[18], Hallberg P[19], Wadelius M[19], Takaoka K[20], Leung YY[21], Bonacina R[22], Schiødt M[23], Lakatos P[24], Taylor T[25], De Riu G[26], Favini G[27], Rogers SN[28], Pirmohamed M[29], Nicoletti P[30]; GENVABO Consortium, Fedele S[1,31].

Collaborators (59)

Author information

Abstract

OBJECTIVES: Osteonecrosis of the jaw (ONJ) is a potentially severe adverse effect of bisphosphonates (BP). Although the risk of ONJ increases with increasing duration of BP treatment, there are currently no reliable estimates of the ONJ time to onset (TTO). The objective of this study was to estimate the TTO and associated risk factors in BP-treated patients.

SUBJECTS AND METHODS: Retrospective analysis of data from 22 secondary care centres in seven countries relevant to 349 patients who developed BP-related ONJ between 2004 and 2012.

RESULTS: The median (95%CI) TTO was 6.0 years in patients treated with alendronate (n = 88) and 2.2 years in those treated with zoledronate (n = 218). Multivariable Cox regression showed that dentoalveolar surgery was inversely associated, and the use of antiangiogenics directly associated, with the TTO in patients with cancer treated with zoledronate.

CONCLUSIONS: The incidence of ONJ increases with the duration of BP therapy, with notable differences observed with respect to BP type and potency, route of administration and underlying disease. When data are stratified by BP type, a time of 6.0 and 2.2 years of oral alendronate and intravenous zoledronate therapy, respectively, is required for 50% of patients to develop ONJ. After stratification by disease, a time of 5.3 and 2.2 years of BP therapy is required for 50% of patients with osteoporosis and cancer, respectively, to develop ONJ. These findings have significant implications for the design of future clinical studies and the development of risk-reduction strategies aimed at either assessing or modulating the risk of ONJ associated with BP.

KEYWORDS: bisphosphonates; breast cancer; jaw osteonecrosis; multiple myeloma; osteoporosis; prostate cancer

PMID: 28039941 DOI: 10.1111/odi.12632

[Indexed for MEDLINE]

Table 3.1 Patient Risk Categories

Low Risk	Higher Risk
If any of the following is present: • Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic glucocorticoids. • Patients being treated for osteoporosis or other non-malignant diseases of bone with quarterly or yearly infusions of intravenous bisphosphonates for **less than 5 years** who are **not** concurrently being treated with systemic glucocorticoids. • Patients being treated for osteoporosis or other non-malignant diseases of bone with denosumab who are **not** being treated with systemic glucocorticoids.	If any of the following is present: • Patients being treated for osteoporosis or other non-malignant diseases of bone (e.g. Paget's disease) with oral bisphosphonates or quarterly or yearly infusions of intravenous bisphosphonates for **more than 5 years.** • Patients being treated for osteoporosis or other non-malignant diseases of bone with bisphosphonates or denosumab **for any length of time** who are being concurrently treated with systemic glucocorticoids. • Patients being treated with anti-resorptive or anti-angiogenic drugs (or both) as part of the management of cancer. • Patients with a previous diagnosis of MRONJ.

Format: Abstract Send to

Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 Feb 14. pii: S2212-4403(18)30072-5. doi: 10.1016/j.oooo.2018.02.003. [Epub ahead of print]

Medication-related osteonecrosis of the jaw: An update on the memorial sloan kettering cancer center experience and the role of premedication dental evaluation in prevention.

Owosho AA[1], Liang STY[2], Sax AZ[3], Wu K[3], Yom SK[3], Huryn JM[3], Estilo CL[4].

Author information

Abstract

OBJECTIVE: The aim of this study was to investigate the relationship between type of antiresorptive medication and medication-related osteonecrosis of the jaw (MRONJ) onset and the role of premedication dental evaluation (PMDE) in the prevention of MRONJ.

STUDY DESIGN: Our database of patients with MRONJ was reviewed. The Kruskal-Wallis test was used to analyze the onset dose of the 3 frequent medication types associated with MRONJ. To evaluate the role of PMDE in the prevention of MRONJ, all patients on antiresorptive and/or antiangiogenic medications seen in the Dental Service of Memorial Sloan Kettering Cancer Center during a 10-year period were subclassified into 2 groups. Group I comprised patients seen for PMDE before the commencement of A/A and group II patients seen after prior exposure to antiresorptive and/or antiangiogenic medications. Fischer's exact test was used to compare the incidence of MRONJ in both groups.

RESULTS: Patients on denosumab developed MRONJ earlier compared with zoledronate and pamidronate ($P = .003$). Group I had a significantly reduced incidence of MRONJ (0.9%) compared with group II (10.5%) ($P < .0001$). Dentoalveolar trauma as a precipitating factor between groups I and II was not statistically significant.

CONCLUSIONS: Denosumab was associated with an earlier occurrence of MRONJ compared with zoledronate and pamidronate. The role of PMDE may be an effective preventive strategy in reducing the incidence of MRONJ.

PMID: 29580668 DOI: 10.1016/j.oooo.2018.02.003

Oral Surg Oral Med Oral Pathol Oral Radiol. 2018 Jan;125(1):27-30. doi: 10.1016/j.oooo.2017.09.014. Epub 2017 Sep 28.

Rapid onset of osteonecrosis of the jaw in patients switching from bisphosphonates to denosumab.

Yarom N[1], Lazarovici TS[2], Whitefield S[3], Weissman T[2], Wasserzug O[4], Yahalom R[2].

Author information

Abstract

OBJECTIVE: The aim of this study was to determine whether osteonecrosis of the jaw (ONJ) developed more rapidly in patients who switched from bisphosphonates (BP) treatment to denosumab than in patients who received only denosumab.

STUDY DESIGN: This was a retrospective cohort study conducted at a tertiary referral center. Thirty-one patients with ONJ met the inclusion criteria.

RESULTS: Twenty-two patients who had been on BP were switched to denosumab (BP + D), whereas 9 patients received only denosumab. Both groups were similar for the known ONJ risk factors, that is, age, diabetes mellitus, and smoking. The number and cumulative doses of denosumab before the onset of ONJ symptoms were significantly lower among the BP + D group compared with the denosumab-only group (P = .025 and .018, respectively). In the BP + D group, ONJ symptoms developed in 9 patients (41%) following the administration of ≤3 denosumab doses compared with ONJ developing in only 1 patient (11%) who was naïve to BP. ONJ developed spontaneously without any known triggering event in 72.7% of patients in the BP + D group and in 77.8% of patients in the denosumab-only group.

CONCLUSIONS: Denosumab-induced ONJ might develop rapidly in patients previously treated with BP. ONJ developed spontaneously in most patients treated with denosumab. In light of our sample being small, there is need for further investigation on our conclusions.

PMID: 29102242 DOI: 10.1016/j.oooo.2017.09.014

non-BR-ONJ _ difference with BRONJ?

- Prevention differences?

Format: Abstract Send to

Evid Based Dent. 2016 Mar;17(1):14-5. doi: 10.1038/sj.ebd.6401149.

Adjusted protocol for dental extractions in oncology patients taking anti-resorptive drugs may reduce occurrence of medication-related osteonecrosis of the jaw.

Borges C[1], Spivakovsky S[2].

Author information

Abstract

DATA SOURCES: PubMed Medline, Embase, LILACS, and reference lists of potential eligible studies.

STUDY SELECTION: Prospective control trials, cohort and case series analysing results on at least 20 patients treated with ARD therapy (IV or orally). Studies reporting a protocol used for dental extraction in patients on ARD; studies reporting data on medically related osteonecrosis of the jaw after dental extraction.

DATA EXTRACTION AND SYNTHESIS: Two review authors independently assessed titles and abstracts for each article identified by the searches in order to decide whether the article was likely to be relevant. After the final selection and before the analyses, authors rated the quality of 13 studies according to a specific study-design-related checklist for each type of study.

RESULTS: Data from 2,566 participants (2098 women and 468 men) were available from 13 selected studies [nine case series, two cohort studies, two randomised clinical trials]. Regarding the mode of administration of bisphosphonates, 21.2% and 79.9% were intravenous (IV) or oral (PO) respectively. The occurrence of MRONJ is statistically higher (P<0.0001) among oncologic patients treated with IV ADR (3.2%, CI=1,7-4,7%) than osteoporotic patients treated with PO ADR (0.15%, CI=0,0-0,36). Alveolectomy compared to non-alveolectomy procedure (P=0.028) and the use of biologic membranes (P=0.015) seems to attenuate the risk of MRONJ after dental extractions. Type of intention was not associated with MRONJ (P=0.32) in both adult IV and PO.

CONCLUSIONS: The authors recommend considering an adjusted protocol for dental extractions in oncological patients taking ARDs to reduce the occurrence of medication-related osteonecrosis of the jaw (MRONJ).

Comment on

Occurrence and risk indicators of medication-related osteonecrosis of the jaw after dental extraction: a systematic review and meta-analysis. [J Clin Periodontol. 2015]

PMID: 27012569 DOI: 10.1038/sj.ebd.6401149

[Indexed for MEDLINE]

Format: Abstract Send to

Int J Oral Maxillofac Surg. 2017 Feb;46(2):151-156. doi: 10.1016/j.ijom.2016.10.009. Epub 2016 Nov 19.

Efficacy of the C-terminal telopeptide test in predicting the development of bisphosphonate-related osteonecrosis of the jaw: a systematic review.

Dal Prá KJ[1], Lemos CA[2], Okamoto R[3], Soubhia AM[4], Pellizzer EP[2].

Author information

Abstract

This systematic review evaluated the efficacy of the morning fasting serum C-terminal telopeptide (CTX) test in predicting the development of bisphosphonate-related osteonecrosis of the jaw (BRONJ). A comprehensive search of studies published up to March 2016, and listed in the PubMed/MEDLINE, Web of Science, and Cochrane Library databases, was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. This review has been registered in the PROSPERO international prospective register of systematic reviews (CRD42016036717). The search identified 542 publications; eight studies were finally deemed eligible for inclusion according to the study criteria. These studies included a total 1442 patients (mean age 66.7 years). The most prescribed drug was alendronate, with osteoporosis being the most frequent indication for the prescription of bisphosphonates. Tooth extraction was the most common trigger for BRONJ. Of all patients evaluated after bisphosphonate treatment, only 24 (1.7%) developed BRONJ. All eight of the selected studies found that CTX levels were not predictive of the development of BRONJ. In conclusion, this systematic review indicates that the CTX test has no predictive value in determining the risk of osteonecrosis in patients taking bisphosphonates.

KEYWORDS: C-terminal telopeptide; CTX; bisphosphonates; osteonecrosis; systematic review

PMID: 27876532 DOI: 10.1016/j.ijom.2016.10.009

[Indexed for MEDLINE]

non-BR-ONJ _ difference with BRONJ?

- Outcome differences?

Cochrane Database Syst Rev. 2017 Oct 6;10:CD012432. doi: 10.1002/14651858.CD012432.pub2.

Interventions for managing medication-related osteonecrosis of the jaw.

Beth-Tasdogan NH[1], Mayer B, Hussein H, Zolk O.

Author information

Abstract

BACKGROUND: Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction experienced by some individuals to certain medicines commonly used in the treatment of cancer and osteoporosis (e.g. bisphosphonates, denosumab and antiangiogenic agents) and involves the progressive destruction of bone in the mandible or maxilla. Depending on the drug, its dosage, and the duration of exposure, the occurrence of this adverse drug reaction may be rare (e.g. following the oral administration of bisphosphonate or denosumab treatments for osteoporosis, or antiangiogenic agent-targeted cancer treatment) or common (e.g. following intravenous bisphosphonate for cancer treatment). MRONJ is associated with significant morbidity, adversely affects quality of life (QoL), and is challenging to treat.

OBJECTIVES: To assess the effects of interventions versus no treatment, placebo, or an active control for the prophylaxis of MRONJ in people exposed to antiresorptive or antiangiogenic drugs.To assess the effects of non-surgical or surgical interventions (either singly or in combination) versus no treatment, placebo, or an active control for the treatment of people with manifest MRONJ.

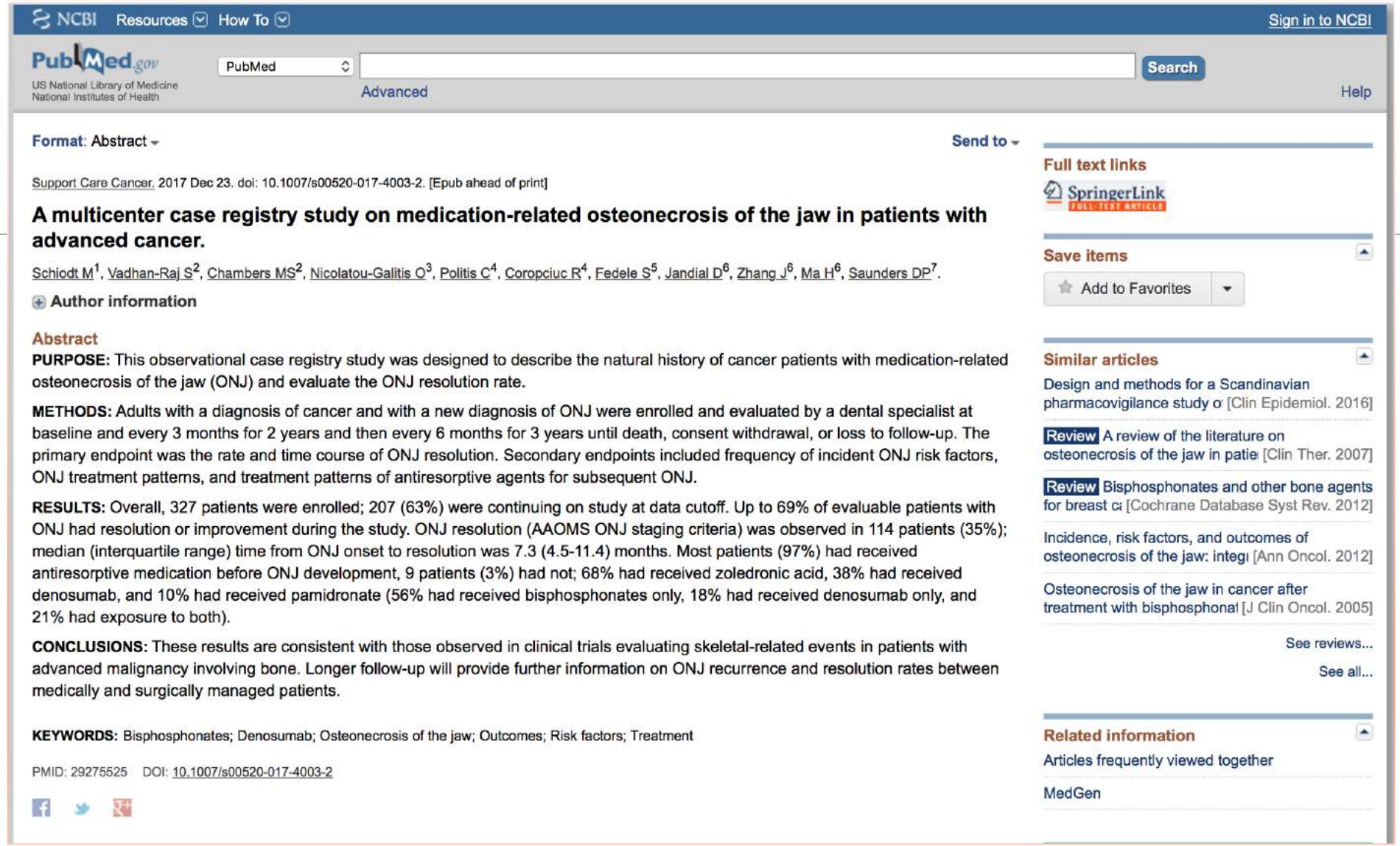
SEARCH METHODS: Cochrane Oral Health's Information Specialist searched the following databases: Cochrane Oral Health's Trials Register (to 23 November 2016), the Cochrane Central Register of Controlled Trials (CENTRAL) (the Cochrane Library, 2016, Issue 10), MEDLINE Ovid (1946 to 23 November 2016), and Embase Ovid (23 May 2016 to 23 November 2016). The US National Institutes of Health Trials Registry (ClinicalTrials.gov) and the World Health Organization International Clinical Trials Registry Platform were searched for ongoing trials. No restrictions were placed on language or publication status when searching the electronic databases; however, the search of Embase was restricted to the last six months due to the Cochrane Embase Project to identify all clinical trials and add them to CENTRAL.

SELECTION CRITERIA: We included randomised controlled trials (RCTs) comparing one modality of intervention with another for the prevention or treatment of MRONJ. For 'prophylaxis of MRONJ', the primary outcome of interest was the incidence of MRONJ; secondary outcomes were QoL, time-to-event, and rate of complications and side effects of the intervention. For 'treatment of established MRONJ', the primary outcome of interest was healing of MRONJ; secondary outcomes were QoL, recurrence, and rate of complications and side effects of the intervention.

DATA COLLECTION AND ANALYSIS: Two review authors independently screened the search results, extracted the data, and assessed the risk of bias in the included studies. For dichotomous outcomes, we reported the risk ratio (RR) (or rate ratio) and 95% confidence intervals (CI).

MAIN RESULTS: We included five RCTs (1218 participants) in the review. Three trials focused on the prophylaxis of MRONJ. Two trials investigated options for the treatment of established MRONJ. The RCTs included only participants treated with bisphosphonates and, thus, did not cover the entire spectrum of medications associated with MRONJ. Prophylaxis of MRONJOne trial compared standard care with regular dental examinations in three-month intervals and preventive treatments (including antibiotics before dental extractions and the use of techniques for wound closure that avoid exposure and contamination of bone) in men with metastatic prostate cancer treated with zoledronic acid. The intervention seemed to lower the risk of MRONJ: RR 0.10; 95% CI 0.02 to 0.39 (253 participants; low-quality evidence). Secondary outcomes were not evaluated.As dentoalveolar surgery is considered a common predisposing event for developing MRONJ, one trial investigated the effect of plasma rich in growth factors (PRGF) for preventing MRONJ in people with cancer undergoing dental extractions. There was insufficient evidence to support or refute a benefit of PRGF on MRONJ incidence when compared with standard treatment (RR 0.08, 95% CI 0.00 to 1.51; 176 participants; very low-quality evidence). Secondary outcomes were not reported. In another trial comparing wound closure by primary intention with wound closure by secondary intention after dental extractions in people treated with oral bisphosphonates (700 participants), no cases of intraoperative complications or postoperative MRONJ were observed. QoL was not investigated. Treatment of MRONJOne trial analysed hyperbaric oxygen (HBO) treatment used in addition to standard care (antiseptic rinses, antibiotics, and surgery) compared with standard care alone. HBO in addition to standard care did not significantly improve healing from MRONJ compared with standard care alone (at last follow-up: RR 1.56; 95% CI 0.77 to 3.18; 46 participants included in the analysis; very low-quality evidence). QoL data were presented qualitatively as intragroup comparisons; hence, an effect estimate of treatment on QoL was not possible. Other secondary outcomes were not reported.The other RCT found no significant difference between autofluorescence- and tetracycline fluorescence-guided sequestrectomy for the surgical treatment of MRONJ at any timepoint (at one-year follow-up: RR 1.05; 95% CI 0.86 to 1.30; 34 participants included in the analysis; very low-quality evidence). Secondary outcomes were not reported.

AUTHORS' CONCLUSIONS: Prophylaxis of MRONJOne open-label RCT provided some evidence that dental examinations in three-month intervals and preventive treatments may be more effective than standard care for reducing the incidence of MRONJ in individuals taking intravenous bisphosphonates for advanced cancer. We assessed the certainty of the evidence to be low.There is insufficient evidence to either claim or refute a benefit of either of the interventions tested for prophylaxis of MRONJ (i.e. PRGF inserted into the postextraction alveolus during dental extractions, and wound closure by primary or secondary intention after dental extractions). Treatment of MRONJAvailable evidence is insufficient to either claim or refute a benefit for hyperbaric oxygen therapy as an adjunct to conventional therapy. There is also insufficient evidence to draw conclusions about autofluorescence-guided versus tetracycline fluorescence-guided bone surgery.



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Support Care Cancer. 2017 Dec 23. doi: 10.1007/s00520-017-4003-2. [Epub ahead of print]

A multicenter case registry study on medication-related osteonecrosis of the jaw in patients with advanced cancer.

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Abstract

PURPOSE: This observational case registry study was designed to describe the natural history of cancer patients with medication-related osteonecrosis of the jaw (ONJ) and evaluate the ONJ resolution rate.

METHODS: Adults with a diagnosis of cancer and with a new diagnosis of ONJ were enrolled and evaluated by a dental specialist at baseline and every 3 months for 2 years and then every 6 months for 3 years until death, consent withdrawal, or loss to follow-up. The primary endpoint was the rate and time course of ONJ resolution. Secondary endpoints included frequency of incident ONJ risk factors, ONJ treatment patterns, and treatment patterns of antiresorptive agents for subsequent ONJ.

RESULTS: Overall, 327 patients were enrolled; 207 (63%) were continuing on study at data cutoff. Up to 69% of evaluable patients with ONJ had resolution or improvement during the study. ONJ resolution (AAOMS ONJ staging criteria) was observed in 114 patients (35%); median (interquartile range) time from ONJ onset to resolution was 7.3 (4.5-11.4) months. Most patients (97%) had received antiresorptive medication before ONJ development, 9 patients (3%) had not; 68% had received zoledronic acid, 38% had received denosumab, and 10% had received pamidronate (56% had received bisphosphonates only, 18% had received denosumab only, and 21% had exposure to both).

CONCLUSIONS: These results are consistent with those observed in clinical trials evaluating skeletal-related events in patients with advanced malignancy involving bone. Longer follow-up will provide further information on ONJ recurrence and resolution rates between medically and surgically managed patients.

KEYWORDS: Bisphosphonates; Denosumab; Osteonecrosis of the jaw; Outcomes; Risk factors; Treatment

PMID: 29275525 DOI: 10.1007/s00520-017-4003-2

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Table 7 ONJ resolution by baseline staging and management

Characteristic	Outcome, *n* (%)					Total (*N* = 327)
	Resolved (*n* = 114)	Improved (*n* = 50)	Progression (*n* = 19)	Stable (*n* = 83)	Not evaluable (*n* = 61)	
Stage at enrollment*						
Resolved†	5 (1.5)	2 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	7 (2.1)
1	28 (8.6)	44 (13.5)	14 (4.3)	0 (0.0)	0 (0.0)	86 (26.3)
2	67 (20.5)	45 (13.8)	74 (22.6)	5 (1.5)	0 (0.0)	191 (58.4)
3	12 (3.7)	1 (0.3)	3 (0.9)	18 (5.5)	0 (0.0)	34 (10.4)
Not evaluable‡	2 (0.6)	3 (0.9)	2 (0.6)	0 (0.0)	2 (0.6)	9 (2.8)
Total	114 (34.9)	95 (29.1)	93 (28.4)	23 (7.0)	2 (0.6)	327 (100.0)
Antiresorptive therapy at baseline						
Denosumab only	26 (41.3)	10 (15.9)	1 (1.6)	14 (22.2)	12 (19.0)	63 (19.3)
Bisphosphonates only	66 (35.5)	26 (14.0)	12 (6.5)	47 (25.3)	35 (18.8)	186 (56.9)
Denosumab plus bisphosphonate	18 (26.1)	13 (18.8)	5 (7.2)	19 (27.5)	14 (20.3)	69 (21.1)
No antiresorptives	4 (44.4)	1 (11.1)	1 (11.1)	3 (33.3)	0	9 (2.8)
Outcomes by management						
Medications only	63 (31.0)	29 (14.3)	10 (4.9)	50 (24.6)	51 (25.1)	203 (62.1)
Medication and surgery	40 (41.2)	21 (21.6)	7 (7.2)	26 (26.8)	3 (3.1)	97 (29.7)
Surgery only	3 (60.0)	0	0	1 (20.0)	1 (20.0)	5 (1.5)
No treatment	8 (36.4)	0	2 (9.1)	6 (27.3)	6 (27.3)	22 (6.7)

*2014 AAOMS staging

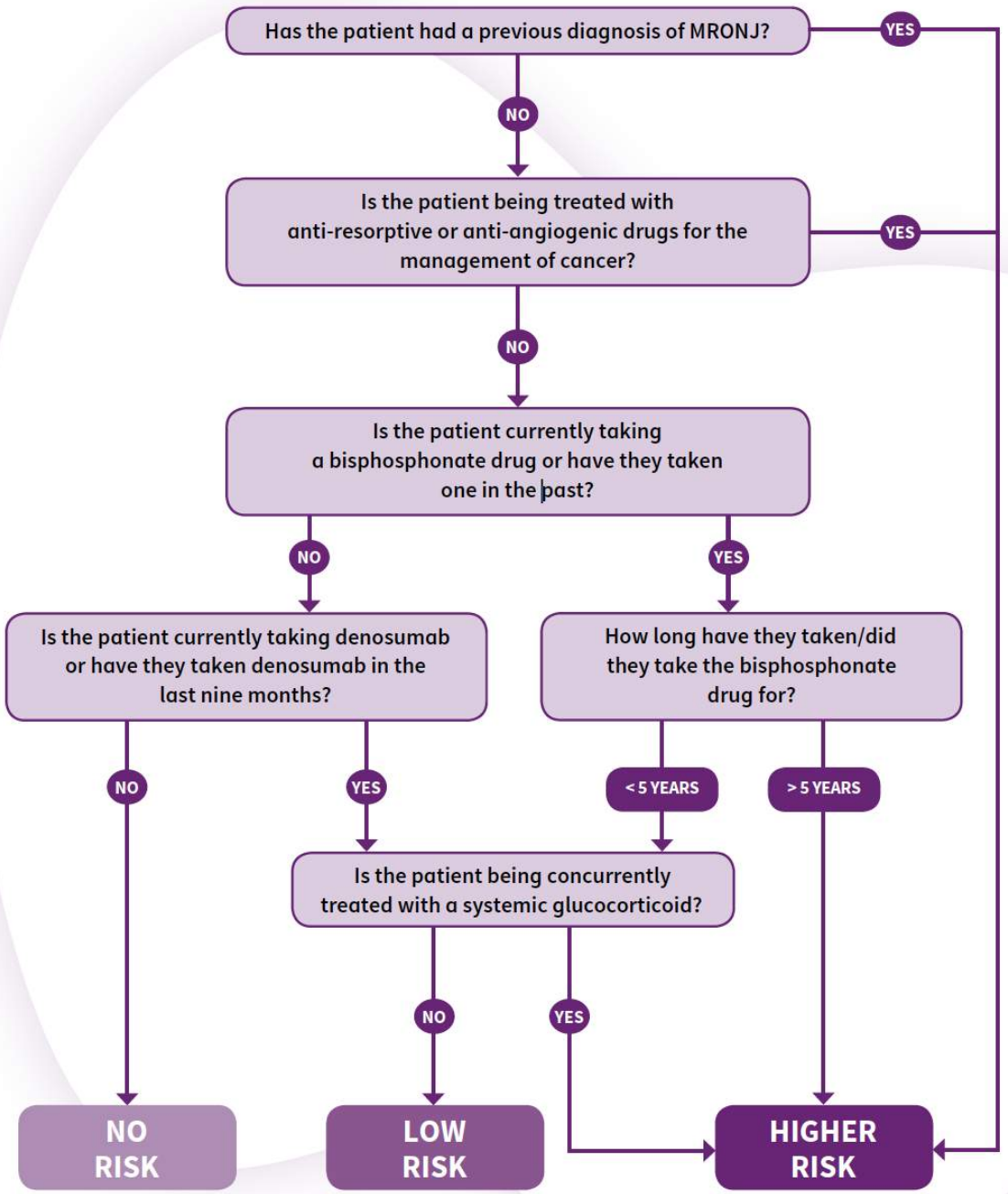
† Patients whose ONJ resolved during the lag time between screening and enrollment. For all criteria, resolution was defined as complete coverage of the exposed bone by mucosa in the absence of clinical symptoms; improvement, progression, and stable were defined by comparing a patient's initial ONJ stage with that at the last available assessment

‡ Patients without any follow-up assessments after enrollment were coded as "not evaluable"

non-BR-ONJ _ Take home message

non-BR-ONJ _ Take home message

- Denosumab, bevacizumab, sunitinib
- < incidence
- Probably differences in the duration of therapy (no dose cumulative)
- Probably better surgical outcome (no data on medical one)
- Difficulties in the correct classification (←) and nomenclature
- New other drugs? ….incoming


Has the patient had a previous diagnosis of MRONJ?
YES
NO
Is the patient being treated with anti-resorptive or anti-angiogenic drugs for the management of cancer?
YES
NO
Is the patient currently taking a bisphosphonate drug or have they taken one in the past?
NO
YES
Is the patient currently taking denosumab or have they taken denosumab in the last nine months?
How long have they taken/did they take the bisphosphonate drug for?
NO
YES
< 5 YEARS
> 5 YEARS
Is the patient being concurrently treated with a systemic glucocorticoid?
NO
YES
NO RISK
LOW RISK
HIGHER RISK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