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REVIEW ARTICLE

Denosumab-related osteonecrosis of the jaw: a systematic review

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Abstract:

Denosumab (DNB) is a human monoclonal antibody, successfully used for the treatment of osteoporosis and some types of malignant neoplasms. Nevertheless, medication-related osteonecrosis of the jaw (MRONJ) is one of its possible side effects. The aim of this study was to summarize the etiology, characteristics, treatment options and prognosis of MRONJ caused by DNB through a systematic review of reported cases. A search was conducted on the Pubmed, Scopus, and Scielo databases, including case reports and case series articles, published until October 2019 about the effect of this drug in the oral and maxillofacial area. Forty-three articles were included, totaling 145 reported cases of MRONJ cases related to DNB. The mean age of the patients was 68.3 years, and the mandible was more affected than the maxilla. The most common triggering factor was dental extractions (60%), although it could happen spontaneously. The prescription of antibiotics and oral rinses, followed by removal of necrotic bone were performed in most articles (106 cases, 73%). In 68.9% of these surgical cases, a total remission of MRONJ was seen. Onset of MRONJ led to discontinuation of denosumab DNB in 42% of the cases. Adjuvant therapies have also been reported to increase treatment success. The increased use of DNB in the treatment of cancer, osteoporosis and other bone conditions highlights the importance of knowing the characteristics DNB-related MRONJ, the possibility of prevention and its treatment options. This review showed that this condition can be controlled with antibiotic therapy, mouthwashes and removal of devitalized bone. Apparently, the use of teriparatide or leucocyte- and platelet-rich fibrin could also contribute to its resolution. However, clinical studies have yet to be performed to support the findings of this systematic review of case reports.

Keywords: Denosumab; RANK Ligand; Osteonecrosis; Adverse effects; Oral medicine.

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INTRODUCTION

Denosumab (DNB) is a human monoclonal IgG_2 antibody, successfully used for osteoporosis treatment[1-3], for the control of some types of malignant neoplasms[4,5] and giant cell granulomas and tumors[6,7]. Its main effect is to prevent bone resorption by inhibiting the receptor activator of nuclear factor-kappa B ligand (RANKL), an essential molecule for osteoclast differentiation, formation, activation and survival[8]. Blocking RANKL binding to its receptor results in significant gain in bone mineral density, rapid reduction in bone turnover markers, and reduced risk of skeletal-related events[9,10].

Clinical studies have shown that DNB has superior effects over zoledronic acid in preventing skeletal-related events in cancer patients[4,10], and similar or slightly superior effects to bisphosphonates in the treatment of osteoporosis[2,3] and giant cell tumors[7]. In addition to its greater efficacy, DNB is believed to produce a more physiological action with fewer side effects than bisphosphonates. And even when present, adverse effects are most rapidly reversed after treatment discontinuation due to the fact that DNB remains in the extracellular matrix, with no evidence of sustained bone binding (half-life of approximately 26 days)[11]. On the other hand, bisphosphonates bind to bone mineral and penetrate osteoclasts, being released for several months or years after stopping bisphosphonate treatment[8].

With the increasing use of DNB around the world, reports of side effects have also started to emerge, including infections (eg, cellulitis and erysipelas), hypocalcemia and medication-related osteonecrosis of the jaw (MRONJ)[5,12], which is characterized by an area of bone exposure that can be probed through intra or extraoral fistula, does not repair for up to 8 weeks and affects patients receiving or that have received angiogenic inhibitors or bone-modifying agents, such as DNB. These patients may not have a history of radiotherapy or evident bone metastasis in the region[13,14].

If misdiagnosed or poorly conducted, MRONJ can become potentially severe and debilitating, impairing patients' quality of life, and often leads to interruption of the treatment of the underlying condition[15]. To date, the DNB-related osteonecrosis of the jaw has been little studied in comparison to the bisphosphonate related one. The aim of this review was to summarize the clinicopathological characteristics, treatment options, and prognosis of MRONJ induced by DNM through a systematic review of cases reported in the pertinent literature.

MATERIAL AND METHODS

For this literature review, a systematic search was conducted in Pubmed, Scopus and Scielo databases, using an association of words related to DNB and the maxillofacial region as search strategy (Table 1). A manual search was also performed in the reference list of the selected articles and relevant reviews identified through the search. We included case reports or case series published until October 2019 about the effect of this drug on the maxillofacial region. No language restrictions were imposed on the search. Studies that did not specify the use of DNB as the only antiresorptive drug being used by the patient at the time of MRONJ development, did not report a case of osteonecrosis, and those that did not have the full text available were excluded.

Table 1. Example of search strategy (Pubmed)

Search	Results
(((((denosumab[Title/Abstract]) OR prolia[Title/Abstract]) OR xgeva[Title/Abstract])))) AND ((((((((((osteonecrosis of the jaw[Title/Abstract]) OR gengival[Title/Abstract]) OR mandib*[Title/Abstract]) OR teeth[Title/Abstract]) OR tooth[Title/Abstract]) OR maxill*[Title/Abstract]) OR oral care[Title/Abstract]) OR oral surgery[Title/Abstract]) OR periodont*[Title/Abstract]) OR oral implant*[Title/Abstract]) OR dent*[Title/Abstract])) NOT review[Publication Type]	233

The electronic search strategy was adapted and applied to Scopus and Scielo

RESULTS

We initially found 233 articles in the Pubmed database, 206 articles in Scopus, 24 articles in Scielo and 1 article in the manual search. After applying the inclusion and exclusion criteria, only 43 articles were included in the present review (Figure 1). Six articles were case series[15-20] and thirty-seven were case reports. Most articles were published in English, except for 3: one published in Spanish[21], one published in French[22] and one published in Italian[23]. United Kingdom, Japan and Spain were the countries with more publications selected for this review with 6 articles each. Germany and the United States published 5 articles each. Belgium and Brazil gave rise to 3 articles each. Two articles came from the Netherlands. Australia, Chile, France, Greece, Italy, Turkey and Korea published 1 article each.

Among the 43 articles included, 145 cases of MRONJ related to DNB were reported. The two articles published by Neuprez et al.[24,25] are a sequence of the same case, so it was counted only once. Table 2 presents the main characteristics of the included articles.

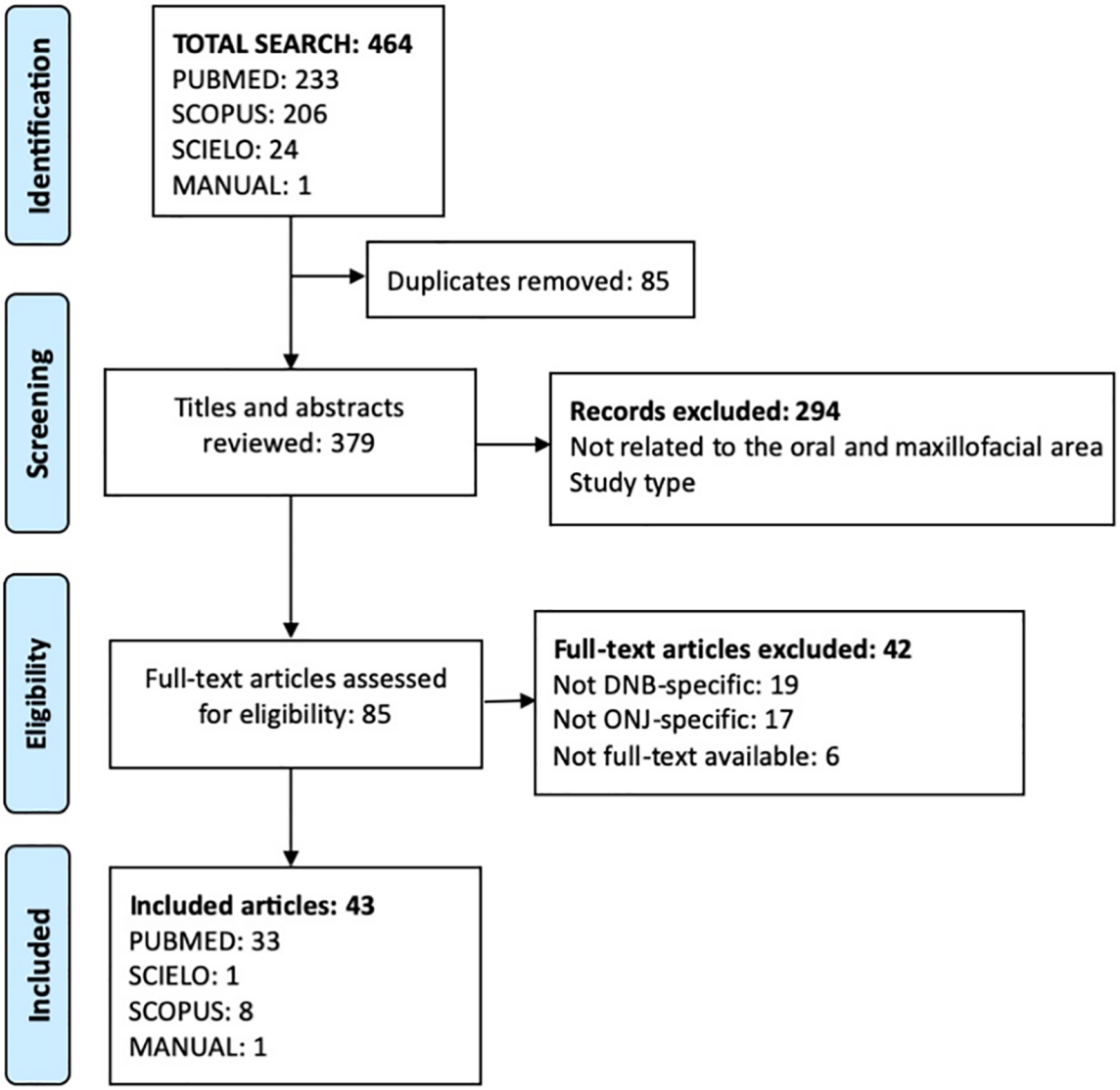

Figure 1. Flow chart of the studies selected for the systematic review.

The average age of the patients with DNB-related MRONJ was 68.3 years, with reports of patients between 19 and 86 years old. Fifty-five of the 145 reported cases (37.9%) had a history of bisphosphonate use prior to initiation of DNB therapy. The mandible was more affected than the maxilla, and the most frequent possible triggering factor was tooth extraction (60% of cases).

In 105 cases (72.4%), DNB was used for cancer treatment (metastatic solid tumors and multiple mieloma). The types of cancer most often treated with DNB were metastatic breast (36.5%) and prostate cancer (27.6%). In 36 cases (24.8%) DNB was used to treat advanced osteoporosis, and in four cases (2.7%) to treat giant cell tumors.

In the majority of included articles, conservative approaches including antibiotic therapy and the use of mouthwashes with chlorhexidine[15,18,19,21,26-40], benzethonium chloride[41] or povidone-iodine mouthwash[42] were employed. Only in five articles the use of some conservative therapy was not reported[11,43-46]. Also, in 61 cases (42%), discontinuation of DNB therapy after MRONJ diagnosis was reported. Within the 26 reported cases treated exclusively with conservative therapies (no surgical approaches), seven (27%) showed total remission of DNB-related MRONJ, five (19%) presented improvement with no total cure within the follow-up period, 11 (42.4%) presented no improvement or worsening of symptoms, two (7.8%) patients lost follow-up and in 1 (3.8%) case the treatment outcome was not reported.

After or concomitant with the use of conservative therapies, most authors employed surgical treatments as bone spicule regularization (1 case[22]), sequestrectomy (17 cases[11,15,20,25,27,30,32,34,35,40,42,44,47-49]) or open debridement with primary closure (88 cases). Total remission of MRONJ was seen after surgical procedures for necrotic bone removal in most studies (73 patients; 68.9% of the surgical cases).

Four articles have reported the use of adjuvant therapies such as injectable teriparatide[21,24] and leucocyte- and platelet-rich fibrin[26,33]. In two articles the fluorescence technique was used to guide bone debridement[16,50] and in two reports a piezo-electric motor for debridement was used[23,26].

Within the 145 cases summarized in the present review, 25 cases (17.2%) showed no improvement or remission of ONM. Two articles reported severe complications: brain abscess[48] and sepsis accompanied by soft palate necrosis[51]. Table 3 presents the treatment strategies and outcomes presented in the included articles.

DISCUSSION

The first case reports of MRONJ were published in the early 2000s as a complication of bisphosphonates therapy. Subsequently, MRONJ was also related to the use of DNB[13,16] and the first reports came from phase III clinical trials testing the effectiveness of DNB in cancer patients[4,10]. In the present work, we proposed a literature review of case reports due to the lack of longitudinal studies focused on diagnosis or treatment of MRONJ caused by DNB.

Previous reviews relating DNB and MRONJ have extracted data from randomized clinical trials whose main objective was to that evaluate the use of this drug on the treatment of giant-cell tumors and cancer patients and reported MRONJ only as an adverse event[52,53]. Qi et al. (2014) analyzed the incidence of developing MRONJ on 8,963 patients with a variety of solid malignant tumors from 7 clinical trials and

Table 2. Characteristics of the included articles

Author, year (Number of cases)	Country	Disease (n)	Dosage (n) (Doses before ONJ)	Affected area (n)	Triggering factor (n)	Stage* (n)
Şahin, 2019[26] (1 case)	Turkey	OP	50 mg; 6/6 months (14 doses)	Maxilla	Tooth extraction	2
Bujaldón-Rodríguez, 2019[27] (1 case)	Spain	OP	60 mg (1 dose)	Mandible	Tooth extraction	2
Yapijakis, 2019[62] (1 case)	Greece	CA	120 mg; 4/4 weeks (6 doses)	Mandible	Tooth extraction	-
de Sales Lima, 2018[44] (1 case)	Brazil	OP	60 mg; 6/6 months (6 doses)	Maxilla	Tooth extraction	2
Aljohani, 2018[16] (63 cases)	Germany	OP (9) CA (54)	120 mg; 4/4 weeks (49) 60 mg; 6/6 months (10) Other therapeutic schemes (3) (Mean: 16,4 ± 12,6 doses)	Mandible (40) Maxilla (17) Both (6)	Tooth extraction (35) Unknown (13) Periodontitis (6) Denture trauma (4) Implant (3) Other (2)	0 (3) 1 (7) 2 (49) 3 (10)
Diniz-Freitas, 2018[28] (1 case)	Spain	OP	60 mg 6/6 months (2 doses)	Mandible	Periodontal scaling	1
Uday, 2018[47] (1 case)	Great Britain	GCT	120 mg at days 1, 8, 15 and 28 + 120 mg every 4 weeks (44 doses)	Mandible	Tooth extraction	2
Ohga, 2018[41] (1 case)	Japan	CA	120 mg monthly (10 doses)	Mandible	Periodontal scaling	2
Sánchez-López, 2018[29] (1 case)	Spain	OP	60 mg 6/6 months (4 doses)	Maxilla	Unknown	2
Martini, 2018[23] (1 case)	Italy	CA	120 mg monthly (19 doses)	Mandible	Denture trauma	1
Badr, 2017[15] (4 cases)	Great Britain	CA	120 mg 6/6 weeks (1) (24 doses) (1)	Mandible (3) Maxilla (1)	Tooth extraction (3) Denture trauma (1)	3 (3) 1 (1)
Yoshimura, 2017[30] (1 case)	Japan	CA	120 mg monthly (7 doses)	Maxilla	Unknown	3
Petkova, 2017[31] (1 case)	Belgium	CA	Not reported (13 doses)	Mandible	Tooth extraction	1
Pichardo, 2016[17] (11 cases)	Holland	OP (4) CA (7)	Monthly CA (7) 6/6 months OP (4) (? doses)	Mandible (7) Maxilla (3) Both (1)	Tooth extraction (10) Peri-implantitis (1)	2 (2) 3 (9)

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de Souza Póvoa, 2016[63] (1 case)	Brazil	CA	120 mg monthly (42 doses)	Mandible	Tooth extraction	1
Lyttle, 2016[32] (1 case)	Great Britain	CA	Monthly (? doses)	Mandible	Tooth extraction	2
Maluf, 2016[33] (2 cases)	Brazil	CA	-	Mandible	Implant (1) Paraendodontic surgery (1)	2
Bagan, 2016[18] (10 cases)	Spain	OP	60 mg 6/6 months (Mean: 3,4 ± 2,2 doses)	Mandible (7) Maxilla (3)	Tooth extraction (6) Implant (1) Denture trauma (1) Spontaneous (2)	1 (8) 2 (2)
Owosho, 2016[19] (13 cases)	United States	CA	120 mg each 4 – 6 weeks (Mean: 15 doses)	Mandible (9) Maxilla (3) Both (1)	Tooth extraction (7) Spontaneous (6)	1 (7) 2 (6)
Matsushita, 2016[43] (2 cases)	Japan	CA	120 mg (? doses)	Mandible (1) Maxilla (1)	Tooth extraction (1) Endodontic treatment (1)	2
Qaisi, 2016[51] (1 case)	United States	OP	Not reported (1 dose)	Mandible	Tooth extraction	3
Yamagata, 2016[48] (1 case)	Japan	CA	120 mg (4 doses)	Both	Unknown	2
Kouketsu, 2016[64] (1 case)	Japan	CA	120 mg monthly (14 doses)	Mandible	Tooth extraction	2
Kyriakidou, 2016[20] (4 cases)	Great Britain	CA	Not reported	Mandible (3) Maxilla (1)	Tooth extraction	2 (2) 3 (2)
You, 2015[34] (1 case)	Korea	CA	120 mg 3/3 weeks (7 doses) + 120mg 3/3 months (2 doses)	Mandible	Tooth extraction	1
Ohga, 2015[42] (1 case)	Japan	CA	120 mg 4/4 weeks (7 doses)	Mandible	Tooth extraction	2
Garcia Garcia, 2015[21] (1 case)	Spain	OP	60 mg (1 dose)	Mandible	Immediate load implant	2
Campos, 2015[45] (1 case)	United States	CA	120 mg monthly (11 doses)	Mandible	Not reported	Not reported
Bodard, 2015[22] (1 case)	France	GCT	120 mg monthly (20 doses)	Mandible	Spontaneous	3
O'Halloran, 2014[35] (2 cases)	Australia	CA	120 mg monthly (Mean: 5 doses)	Mandible (1) Maxilla (1)	Tooth extraction (1) Unknown (1)	2 (1) 3 (1)
Olate, 2014[36] (1 case)	Chile	CA	60 mg (? doses)	Mandible	Tooth extraction	2
Neuprez 2014a 25, 2014b[24] (1 case)	Belgium	OP	60 mg 6/6 months (1 dose)	Mandible	Tooth extraction	2
Vyas, 2014[46] (1 case)	Great Britain	OP	60 mg 6/6 months (10 doses)	Mandible	Tooth extraction	2
Aghaloo, 2014 [49] (1 case)	United States	GCT	120 mg 3/3 months (3 doses) + 120 mg each 1–2 months for 1 year (? doses)	Mandible	Unknown	0
Moysich, 2014[65] (1 case)	Germany	CA	Not reported	Mandible	Tooth extraction	2
Rashad, 2013[66] (1 case)	Germany	OP	60 mg 6/6 months (6 doses)	Mandible	Tooth extraction + denture trauma	0
Otto, 2013[50] (2 cases)	Germany	OP	60 mg 6/6 months (? doses)	Mandible	Tooth extraction (1) Implant (1)	2
Pichardo, 2013[11] (1 case)	Holland	CA	Not reported	Mandible	Unknown	3
Rachner, 2013[67] (1 case)	Germany	OP	60 mg (1 doses)	Mandible	Unknown	-
Diz, 2012[38] (1 case)	Spain	CA	120 mg 4/4 weeks (17 doses)	Mandible	Tooth extraction	2
Aghaloo, 2010[39] (1 case)	United States	GCT	120 mg weekly for 3 weeks + 120 mg 4/4 weeks (? doses)	Mandible	Endodontic treatment	2
Taylor, 2010[40] (1 case)	Great Britain	CA	Not reported	Mandible	Unknown	2

OP: osteoporosis, CA: cancer, GCT: Giant cell tumor, DNB: denosumab, ONJ: osteonecrosis of the jaw; * Staging according to Ruggiero et al., 2014[13] and Yarom et al., 2019[14].

Table 3. Treatments and outcomes described the included articles

Author, year (Number of cases)	Treatment (n)	Outcome (n)
Şahin, 2019[26] (1 case)	Surgical treatment (necrotic bone removal with piezo-electric motor + leucocyte- and platelet-rich fibrin application + primary closure) Chlorhexidine mouthwash Antibiotic therapy (amoxicillin/clavulanic acid 1000 mg + metronidazole 500 mg)	Resolution within 3 weeks
Bujaldón-Rodríguez, 2019[27] (1 case)	Spontaneous sequestrectomy Chlorhexidine mouthwash (3 times/day) Antibiotic therapy (clindamycin 3 x 300 mg/day for 14 days)	Resolution within 2 weeks
Yapijakis, 2019[62] (1 case)	Surgical debridement Antibiotic therapy (ciprofloxacin 2 x 500 mg/day + metronidazole 3 x 500 mg/day)	-
de Sales Lima, 2018[44] (1 case)	Sequestrectomy	Resolution without recurrence within 8 months
Aljohani, 2018[16] (63 cases)	Surgical treatment (antibiotic therapy + necrotic bone removal + primary closure) (60): - fluorescence guided surgery (27) - conventional surgery (38) - curettage (1) Conservative treatment (3) DNB suspension (42)	Surgical treatment led to resolution in 71.7%, improvement in 11.3%, and no cure in 17% of the cases. Complete resolution in 2 out of 3 conservatively-treated cases. No cure in 1 case.
Diniz-Freitas, 2018[28] (1 case)	Surgical treatment (necrotic bone removal + primary closure) Chlorhexidine mouthwash (twice a day) Antibiotic therapy (doxycycline 200 mg/day for 4 weeks)	Resolution without recurrence at 6-month follow-up
Uday, 2018[47] (1 case)	Antibiotic therapy (amoxicillin + metronidazole) Mouthwash Sequestrectomy	Resolution without recurrence at 18-month follow-up
Ohga, 2018[41] (1 case)	DNB suspension Antibiotic therapy Benzethonium chloride mouthwash	Resolution 36 weeks after DNB interruption
Sánchez-López, 2018[29] (1 case)	DNB suspension Antibiotic therapy (amoxicillin 3 x 1 g/day for 7 days) Chlorhexidine mouthwash (3 times/day)	Improvement with no total cure within 1 year of follow-up
Martini, 2018[23] (1 case)	DNB suspension Non-use of the prosthesis Antibiotic therapy (amoxicillin with clavulanic acid 3 x 1 g/day + metronidazole 4 x 250 mg/day for 10 days) Surgical treatment (necrotic bone removal + primary closure)	Resolution
Badr, 2017[15] (4 cases)	Lost follow up (1) Antibiotic therapy (3) Chlorhexidine mouthwash (2) Sequestrectomy (2) DNB suspension (2)	Clinical improvement (1) Not reported (3)
Yoshimura, 2017[30] (1 case)	Antibiotic therapy (amoxicillin 750 mg/day for 7 days) Chlorhexidine mouthwash Sequestrectomy (patient denied more invasive surgical treatment)	Decreased pain at 30-month follow-up
Petkova, 2017[31] (1 case)	Chlorhexidine mouthwash	Not reported
Pichardo, 2016[17] (11 cases)	Antibiotic therapy (penicillin G 6 x 1 million IU/day + metronidazole 3 x 500 mg/day IV + oral amoxicillin 3 x 500 mg/day + metronidazole 3 x 500 mg/day for 3 weeks). Surgical treatment (necrotic bone removal + primary closure)	Resolution after 4 weeks of treatment (9) No resolution (2)
de Souza Póvoa, 2016[63] (1 case)	DNB suspension Surgical treatment (necrotic bone removal + primary closure) Antibiotic therapy (amoxicillin 3 x 500 mg/day for 7 days) Local chlorhexidine gel	Resolution without recurrence at 26-month follow-up
Lyttle, 2016[32] (1 case)	DNB suspension Antibiotic therapy (amoxicillin 3 x 500 mg/day + metronidazole 3 x 200 mg/day for 5 days) Chlorhexidine mouthwash Sequestrectomy	Resolution

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Maluf, 2016[33] (2 cases)	DNB suspension Antibiotic therapy (Penicilin/Clavulanate 875 mg) Chlorhexidine mouthwash (Twice a day) Surgical treatment (necrotic bone removal + leucocyte- and platelet-rich fibrin application + primary closure)	Improvement with no total cure within 6 months of follow-up
Bagan, 2016[18] (10 cases)	Chlorhexidine mouthwash (10) Antibiotic therapy (9) (doxycycline 2 x 100 mg/day for 10 days) Surgical debridement (1)	Resolution (5) No resolution (2) Loss of follow up (2) Rejected treatment (1)
Owosho, 2016[19] (13 cases)	Chlorhexidine mouthwash (2 to 3 times per day) Antibiotic therapy when indicated	Death (1) Loss of follow up (2) Resolution (3) Improvement with no total cure (1) Unchanged condition (2) Disease progression (4)
Matsushita, 2016[43] (2 cases)	Surgical resection of necrotic bone	Resolution without recurrence at 6-month follow-up
Qaisi, 2016[51] (1 case)	Antibiotic therapy (vancomycin, levofloxacin, and meropenem + 4-week ampicillin/sulbactam + oral amoxicillin/clavulanate)	Improvement with no total resolution
Yamagata, 2016[48] (1 case)	Antibiotic therapy (ceftriaxone 2 x 2 g/day + metronidazole 3 x 500 mg/day for 50 days) Sequestrectomy	Not reported
Kouketsu, 2016[64] (1 case)	Abscess drainage Antibiotic therapy (penicillin G 6 × 40,000 U/day) Surgical debridement	Improvement with no total resolution
Kyriakidou, 2016[20] (4 cases)	Not reported (1) DNB suspension (2) Antibiotic therapy (2) Sequestrectomy (1) Surgical debridement (1)	Not reported (2) Resolution (1) Improvement with no total resolution (1)
You, 2015[34] (1 case)	Chlorhexidine mouthwash (Twice a day) Sequestrectomy	Resolution without recurrence
Ohga, 2015[42] (1 case)	DNB suspension Povidone-iodine mouthwash Antibiotic therapy (Cefditoren pivoxil) Sequestrectomy	Resolution
Garcia Garcia, 2015[21] (1 case)	DNB suspension Antibiotic therapy (amoxicillin with clavulanic acid 3 x 875 mg/day for 15 days) Chlorhexidine mouthwash (2-3 times/day) Subcutaneous teriparatide 20 mg/day for 6 months	Resolution after 8 months of treatment
Campos, 2015[45] (1 case)	Not reported	Not reported
Bodard, 2015[22] (1 case)	Antibiotic therapy (itraconazole, pristinamycin and ertapenem) Bone spicule regularization	No resolution
O'Halloran, 2014[35] (2 cases)	DNB suspension Antibiotic therapy Chlorhexidine mouthwash Sequestrectomy	Resolution (1) Improvement with no total resolution (1)
Olate, 2014[36] (1 case)	DNB suspension Chlorhexidine mouthwash (daily)	No resolution within 6 months of follow-up
Neuprez 2014a[25], 2014b[24] (1 case)	DNB suspension Antibiotic therapy Sequestrectomy Subcutaneous teriparatide 20 mg/day for 6 months	Improvement after130 days of treatment
Vyas, 2014[46] (1 case)	DNB suspension	Resolution in 1 month
Aghaloo, 2014[49] (1 case)	DNB suspension Sequestrectomy Antibiotic therapy (amoxicillin 3 x 500 mg/day) Chlorhexidine mouthwash (twice a day)	Not reported

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Moysich, 2014[65] (1 case)	Antibiotic therapy Surgical treatment (necrotic bone removal + primary closure)	Resolution
Rashad, 2013[66] (1 case)	Antibiotic therapy (ampicillin/sulbactan)	Slight pain improvement in 2 months
Otto, 2013[50] (2 cases)	Antibiotic therapy (doxycycline 2 x 100 mg for 10 days preoperatively) Fluorescence-guided surgery (necrotic bone removal + primary closure)	Resolution after months of treatment
Pichardo, 2013[11] (1 case)	Sequestrectomy	No resolution
Rachner, 2013[67] (1 case)	Surgical debridement Antibiotic therapy	Resolution without recurrence at 14-month follow-up
Diz, 2012[38] (1 case)	Antibiotic therapy (amoxicillin) Chlorhexidine mouthwash Surgical debridement Periodic sequestrectomies Surgery (necrotic bone removal + primary closure)	Resolution without recurrence
Aghaloo, 2010[39] (1 case)	Antibiotic therapy (clindamycin 4 x 300 mg/day) Chlorhexidine mouthwash (twice a day)	No remission until date of death
Taylor, 2010[40] (1 case)	DNB suspension Antibiotic therapy (amoxicillin 3 x 500 mg/day for one week) Chlorhexidine mouthwash Sequestrectomy	Resolution without recurrence at 15-month follow-up

DNB: denosumab

observed a 1.7% incidence of MRONJ[52]. Boquete-Castro et al. (2016) also included 7 clinical trials, 1 in giant-cell tumor patients and the other in oncologic patients, observing the same 1.7% incidence of MRONJ[53]. Both studies found that the use of denosumab was associated with a significantly increased risk of MRONJ in comparison with bisphosphonates. None included patients using DNB in the osteoporosis protocol.

In the present work, it was observed that in most cases MRONJ started from surgical dental procedures (extraction, implant installation, periodontal scaling, paraendodontic surgery), however, the appearance of MRONJ in prosthetic trauma sites, after endodontic treatment and even spontaneously developed cases were observed. The appearance of MRONJ in the absence of previous surgical procedures can be corroborated in the literature. Watts et al. (2019) found a MRONJ incidence of 0.68% (11/1621 patients) in DNB-treated women with osteoporosis who reported previous invasive oral procedures, and a 0.05% incidence (1/1970 patients) in women who reported no previous invasive procedure[54]. In another case-control study it was found that non-surgical and surgical dental treatments, such as dental extractions, were significantly associated with the development of MRONJ[55].

We also observed that the therapeutic recommendations of Ruggiero et al. (2014)[13] according to the disease's stage, are not followed by many professionals. While some authors insert surgical procedures already in stage I, others prefer conservative treatments even in more advanced stages. Despite these treatment differences, only 18% of the reported cases showed no improvement.

The use of supporting techniques and materials was also observed in this review. Leucocyte- and platelet-rich fibrin were used in two case reports in conjunction with the removal of necrotic bone to treat stage II MRONJ[26,33]. This is a physiological material that incorporates leukocyte and platelet concentrate, allowing the release of growth factors over a prolonged time, accelerating the healing and remodeling rate of soft and hard tissues, and reducing the contamination risk, edema and postoperative pain[56]. In the study of Maluf et al. (2016) both cases showed improvement, but without total cure in 6 months of follow-up[33]. In the case reported by Sahin et al. (2019), complete epithelialization was achieved within 3 weeks[26]. In another article, Kim et al. (2019) treated 39 bisphosphonate MRONJ patients with surgical debridement and leucocyte- and platelet-rich fibrin application. They found that 77% of patients had complete resolution, 18% had late resolution and 6% did not resolve within 4 months of follow-up[57].

Teriparatide, a human peptide consisting of amino acids present in parathyroid hormone, was also used as an adjuvant in two cases of stage II MRONJ. An intermittent infusion of teriparatide results in anabolic effects in bone, increasing bone formation earlier and to a greater degree than resorption, leading to positive bone balance[58]. In the present work, we saw that one case showed cure after 8 months of treatment[21]

and the other showed improvement after approximately 4 months of teriparatide treatment[24]. Positive effects have also been reported in the literature with the use of teriparatide. Kim et al. (2014) observed a more favorable response in cases of intracTable MRONJ conducted with teriparatide, compared to patients who did not receive this hormone[59]. Kakehashi et al. (2015) evaluated the effect of daily teriparatide injections on the treatment of bisphosphonate-related jaw osteonecrosis and observed improvement in 7 of 10 treated cases[60].

We also saw that the onset of MRONJ led to discontinuation of DNB treatment in 43% of cases. In these articles it was not reported whether the suspension of DNB caused any damage or progression of the underlying disease. Studies show that after discontinuation of denosumab for more than 6 months, bone turnover rebound increases and bone density decreases rapidly, leading to an increased risk of fractures[61].

CONCLUSION

The increased use of DNB in the treatment of cancer, osteoporosis and other bone conditions and, therefore, the increased incidence of osteonecrosis of the jaw caused by this drug, highlights the importance of knowing the characteristics of this pathology, the possibility of prevention and its treatment options. This review showed that DNB-related MRONJ can occur even in the absence of surgical procedures in the oral cavity and is more common in the mandible. In most cases, DNB-related osteonecrosis of the jaw can be controlled with antibiotic therapy, mouthwashes and removal of devitalized bone. Apparently, the use of teriparatide or leucocyte-and platelet-rich fibrin could contribute to resolution of the condition. However, clinical studies have yet to be performed to support the findings of this systematic review of case reports.

CONFLICT OF INTEREST

There are no conflicts of interest regarding the publication of this paper.

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