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REVIEW

Stage-specific therapeutic strategies of medication-related osteonecrosis of the jaws: a systematic review and meta-analysis of the drug suspension protocol

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Abstract

Objective The most debated topic about medication-related osteonecrosis of the jaws (MRONJ) is its therapy, as there are no definitive guidelines. The aims of this systematic review were (a) to outline the best therapeutic approach according to the stage at diagnosis and (b) to perform a meta-analysis to assess whether the drug-holiday protocol may be or not an effective method in the management of MRONJ patients.

Materials and methods The systematic review was performed following the PRISMA principles. Results were screened according to inclusion and exclusion criteria regarding staging before/after treatment, follow-up, and information provided by the authors. For statistical analysis, linear variables are reported as means and standard deviations, medians, and inter-quartile range (IQR); normality of data, according to the distribution of complete healing (primary outcome variable), was assessed with the Kolmogorov-Smirnov test. A p value < 0.05 was considered statistically significant for all tests.

Results Thirteen studies were selected out of 1480. None of them was case-controlled or randomized. Conservative approach showed good results at early stages, but heterogeneous result at advanced stages (100% stage 0, stage I range 81–97%, stage II range 63.6–100%, stage III 73%). Surgical approach showed heterogeneous results at all stages (stage I range 0–100%, stage II range 52–100%, stage III range 50–100%). Statistical analysis showed a significantly higher prevalence of completely healed sites in patients who followed the drug-holiday protocol.

Conclusions The results suggest that the current stage-specific approach for MRONJ therapy is based on a sound clinical rationale. Conservative treatment appears to yield better outcomes at early stages, while further investigations are needed to elucidate the best protocols for the management of advanced stages. The drug-holiday protocol statistically promotes complete healing after oral surgery procedures but the application should be dictated by the condition of each patient.

Clinical relevance At present, early MRONJ stages should be primarily treated by means of a conservative approach while more advanced stages must be carefully evaluated. Individual decisions should be made for every single case even with respect to the drug-holiday protocol.

Keywords Osteonecrosis · Bisphosphonates · BRONJ · ARONJ · MRONJ · Drug-holiday protocol

Introduction

Bisphosphonates (BPs) are a drug class used for treatment of many different pathologies causing loss of bone mass, e.g., Paget's disease, osteoporosis, multiple myeloma, and bone metastasis from different solid tumors, and direct or indirect antitumoral action [1–5].

Possible complication of BP therapy is bisphosphonate-related osteonecrosis of the jaws (BRONJ), described for the

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first time in 2003 [6] and then reported in an increasing number of clinical studies. This condition is defined as an exposition of necrotic bone in the oral cavity lasting more than 8 weeks, in patients who took BPs and have not been exposed to head and neck radiotherapy [7, 8].

In 2010, it was reported for the first time an osteonecrosis of the jaws (ONJ) case in a patient who did not take BPs but had been administered denosumab, a bone resorption inhibitor (anti-resorptive agent, ARA) with a mechanism of action similar to BPs [9]. This observation has led to redefining the concept of BRONJ, thus preferring the new and wider denomination of anti-resorptive-related osteonecrosis of the jaws (ARONJ).

Furthermore, various case reports have recently shown that in small percentages of patients who did not take any kind of anti-resorptive drugs, anti-angiogenic drugs may cause ONJ. In the light of these considerations, in 2014, the concept of medication-related osteonecrosis of the jaws (MRONJ) has been introduced, thus providing a wide definition, encompassing not only anti-resorptive agents but also anti-angiogenic drugs [10]. MRONJ, similarly to BRONJ, is defined as an exposition of necrotic bone in the oral cavity lasting more than 8 weeks, in patients who took anti-resorptive or anti-angiogenic drugs and have not been exposed to head and neck radiotherapy, and have no bone metastases in the maxillofacial region [10].

Up until today, anti-resorptive and anti-angiogenic drugs reported to cause medication-related osteonecrosis of the jaws, in addition to BPs, are the following: denosumab [9, 11] (a monoclonal antibody indicated for osteoporosis treatment, kidney cancer, and prostatic cancer, whose mechanism of action is the inhibition of RANKL), bevacizumab [12, 13] (monoclonal antibody able to bind and selectively inhibit VEGF-A, a vascular growing factor which is hyper-expressed in various tumors), temsirolimus [12] (specific mTOR inhibitor), sunitinib [13, 14] (tyrosine kinase inhibitor administered to treat renal cell carcinoma and gastrointestinal stromal tumor). The potential risk associated with drugs from the same class or with a similar mechanism of action must not be underestimated; continuous surveillance is needed to identify any molecule which may cause ONJ [7].

The most debated topic about medication-related osteonecrosis of the jaws is the therapy. MRONJ is triggered by local trauma (minor oral surgery or chronic traumatism due to ill-fitting prosthesis) or may be spontaneous, caused by dental or periodontal infections [15, 16]. Thus, prevention of MRONJ is feasible by using a multidisciplinary approach and detection of dental foci prior to starting any anti-resorptive/anti-angiogenic therapy followed by continuous monitoring of dental diseases.

On the contrary, once this condition begins, there is no standardized therapeutic protocol [10]. When treated ineffectively, MRONJ may be a dramatically invalidating disease, as bone exposition is often complicated by secondary infections leading to osteomyelitis, abscesses, fistulae, and/or pathological fractures. These conditions have a substantial impact on patient's life quality by impairing speaking, eating, and swallowing.

It has to be noted that the proposed various treatment approaches are rather based on personal experience than on scientific evidence.

In general, there are two main options to treat MRONJ (e.g., either conservatively with antibiotics and antiseptics or surgically by removing necrotic bone with different grades of aggressiveness, from the sole debridement to segmental resection, reconstructing with free/pediculated flaps if needed) [17–19]. Although many different approaches with heterogeneous results have been proposed, a generally widespread concept, underlined also in the latest consensus conferences, is that therapy should be stage-specific [10].

The American Association of Oral and Maxillofacial Surgeons (AAOMS) has classified MRONJ into four stages [10, 20] (Table 1), characterized by the increasing extent of the lesions, involvement of noble structures, pain, and symptoms (Figs. 1, 2, 3, and 4). The conclusions from consensus conference suggest that conservative approach should be preferred for initial stages (0, I), while a more aggressive approach should be chosen on the advanced ones (II, III) [10].

Still, even if stage-specific therapy has reached general agreement, precise treatment guidelines are neither available for the conservative/medical approach by specifying what antibiotics/antiseptics should be preferred nor for the surgical approach, precisely defining what kind of intervention should be adopted (e.g., debridement, conservative resection, or segmental resection with/without reconstructive free/pediculated flap) [10].

It is, however, important to point out that at present, there is no scientific evidence from systematic reviews including meta-analysis, on the preferred treatment approach according to the MRONJ stages.

Thus, the aims of the systematic review were (a) to find a validation of this method and to outline the best therapeutic approach according to the stage at diagnosis and (b) to perform a meta-analysis in order to assess whether the drug-holiday protocol may be or not an effective method in the management of MRONJ patients.

Materials and methods

This systematic review was performed following the PRISMA principles (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) [21].

Focused question

The most debated topic about MRONJ is the therapy, as there are no definitive guidelines. Conclusions of the latest consensus conference suggest that a stage-specific approach could be more adequate but still remains unclear the best stage-specific

Table 1 MRONJ staging according to AAOMS

Stage	Features
0	Unspecific radiographic signs related to the disease and pain without exposed bone (unexposed bone variant)/patients with history of MRONJ.
I	Necrotic bone exposed in oral cavity (or presence of bone-mucosa fistula through which bone may be probed trans-orally), for more than 8 weeks, in an asymptomatic patient and with no evidence of clinical infection.
II	Necrotic bone exposed in oral cavity (or presence of bone-mucosa fistula through which bone may be probed trans-orally), for more than 8 weeks, in patient with pain and clinical evidence of infection.
III	Necrotic bone exposed in oral cavity (or presence of bone-mucosa fistula through which bone may be probed trans-orally), for more than 8 weeks, in patient with pain and clinical evidence of infection and at least one of the following: extension of necrotic area or osteolysis over the alveolar process (ramus or inferior margin of the mandible, maxillary sinus, zygomatic arch), pathological fracture, extra-oral or oroantral or oronasal fistula.

approach and the role of drug-holiday protocols in reducing the occurrence of adverse events after oral surgery procedures.

Therefore, the focus question for this review and meta-analysis, developed using the PICO (population, intervention, comparison, outcome) criteria, was as follows: "Do the stage-specific approach represent the best treatment and the drug-holiday protocol promote complete healing after oral surgery procedures in MRONJ patients?"

The PICO criteria used were as follows:

Population: patients assuming bisphosphonates candidate for oral surgery procedures
Intervention: drug-holiday protocol before oral surgery procedures
Comparison: no cessation of bisphosphonates before surgical therapy
Outcome: complete healing of hard and soft tissues

Search strategy

The search was conducted on electronic databases up to June 2016. The search was applied to the Cochrane Oral Health Group specialist trials, MEDLINE, Scopus, and Web of Science.

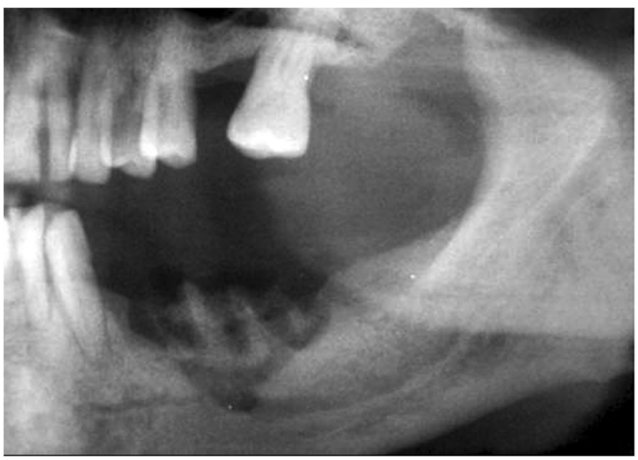

Fig. 1 Stage 0: OPT radiographic evidence of mandibular osteonecrosis

The strategy used was a combination of MeSH (Medical Subject Headings) terms and free text words: "ONJ" [text word] AND "oral surgery" [MeSH], "ONJ" [text word] AND "conservative therapy" [text word], "ONJ" [text word] AND "after treatment" [MeSH] OR "adverse event" [MeSH], "BRONJ" [text word] AND "oral surgery" [MeSH], "BRONJ" [text word] AND "after treatment" [MeSH] AND "complication postoperative" [MeSH], "osteonecrosis" [MeSH] AND "staging" [MeSH], "osteonecrosis" [MeSH] AND "oral surgery" [MeSH], "osteonecrosis" [MeSH] AND "antiresorptive drugs" [MeSH] AND "Antiangiogenic Agents" [MeSH], "bisphosphonate" [MeSH] AND "BRONJ" [text word] OR "osteonecrosis" [MeSH], "ARONJ" [text word] AND "bisphosphonate" [MeSH] AND "therapy" [text word], "MRONJ" [text word] AND "oral surgery" [MeSH] AND "complication postoperative" [MeSH], "MRONJ" [text word] AND "conservative therapy" [text word], "MRONJ" [text word] AND "staging" [MeSH] AND "therapy" [text word], "MRONJ" [text word] AND "antiresorptive drugs" [MeSH] AND "therapy" [text word], "MRONJ" [text word] AND "complication postoperative" [MeSH], "MRONJ" [text word] AND "Antiangiogenic Agents" [MeSH] AND "therapy" [text word].

Inclusion criteria

The studies were included on the basis of the following criteria:

- English language
- Lesions were staged prior to start of treatment according American Association of Oral and Maxillofacial Surgeons (AAOMS) medication-related osteonecrosis of the jaws classification
- Results obtained were related to AAOMS medication-related osteonecrosis of the jaws staging at diagnosis

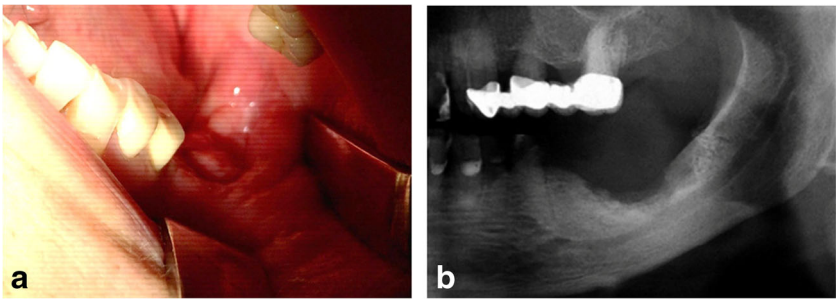

Fig. 2 Stage 1: **a** necrotic bone exposed in the left posterior mandibular region in an asymptomatic patient. **b** OPT radiographic evidence of mandibular osteonecrosis

- Length of follow-up and therapeutic approach (administered antibiotics and antiseptics/surgical technique) was stated clearly
- Success was evaluated with complete mucosal healing, bone covering, and remission of symptoms
- Detailed information about medical treatment—which had to be concluded at the time of the study—that caused medication-related osteonecrosis of the jaws

Exclusion criteria

The studies were excluded on the basis of the following criteria:

- Patients' follow-up was shorter than a month or not specified
- Primary disease was a malignant disease directly involving the jaws
- Complete healing outcome data were mixed with other outcome data (e.g., improvement or stationary)
- Treatment performed was considered unconventional in the latest American Association of Oral and Maxillofacial Surgeons (AAOMS) consensus conference (platelet-rich plasma [PRP] alone, low-level laser therapy [LLLT], parathyroid hormone, bone morphogenetic protein, mesenchymal stem cells, hyperbaric oxygen therapy)
- Absence of original clinical study (e.g., reviews, meta-analyses, case reports)
- Studies based on questionnaire or interview
- Radiographic studies
- Studies with only histological data
- Animal studies

Data extraction and analysis

The titles identified by the search were screened independently by two reviewers (I.S.V. and G.A.). The abstracts of all possibly relevant studies were obtained and screened independently by the reviewers. When studies met the inclusion criteria or when insufficient data from abstracts were available to evaluate inclusion criteria, the full-text article was obtained. In case of articles concerning consecutive phases of the same study or extension of the original sample, only one article with the most recent data was considered (longest follow-up and/or largest sample).

The selected papers were screened independently by the two reviewers to confirm whether they met or not, the inclusion criteria. The inter-examiner agreement was analyzed by kappa coefficient. Any discrepancy between the two reviewers was resolved via discussion. Data were extracted independently by the two examiners (I.S.V. and G.A.).

If the reviewers had data-related questions, the authors of the selected papers were contacted directly.

Statistical analysis

Linear variables are reported as means and standard deviations, medians, and inter-quartile range (IQR) while categorical and dichotomous variables are reported as percentages.

Normality of data, according to the distribution of complete healing (primary outcome variable), was assessed with the Kolmogorov-Smirnov test in order to choose between parametric and non-parametric analysis.

A comparison of complete healing rates between patients enrolled in drug-holiday protocols and patients belonging to non-drug-holiday protocols was performed using the Pearson

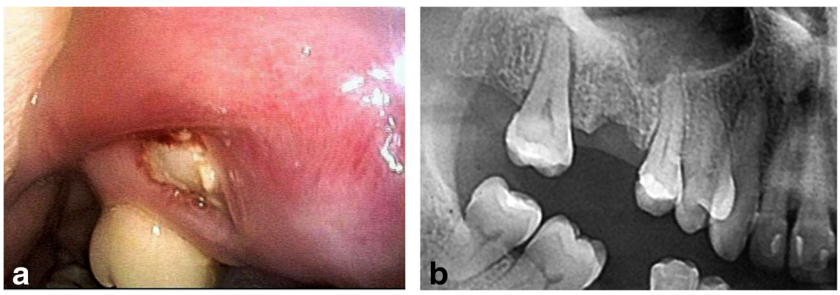

Fig. 3 Stage 2: **a** necrotic bone exposed in the right posterior maxillary region, in patient with pain and clinical evidence of infection. **b** OPT radiographic evidence of maxillary osteonecrosis

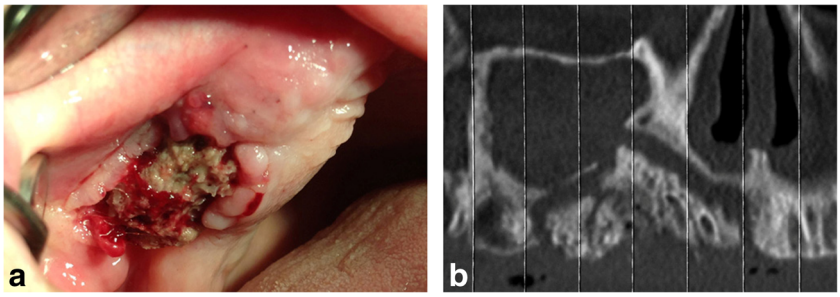

Fig. 4 Stage 3: **a** necrotic bone exposed in the right posterior maxillary region with oroantral fistula. **b** CT radiographic evidence of maxillary osteonecrosis with oroantral fistula

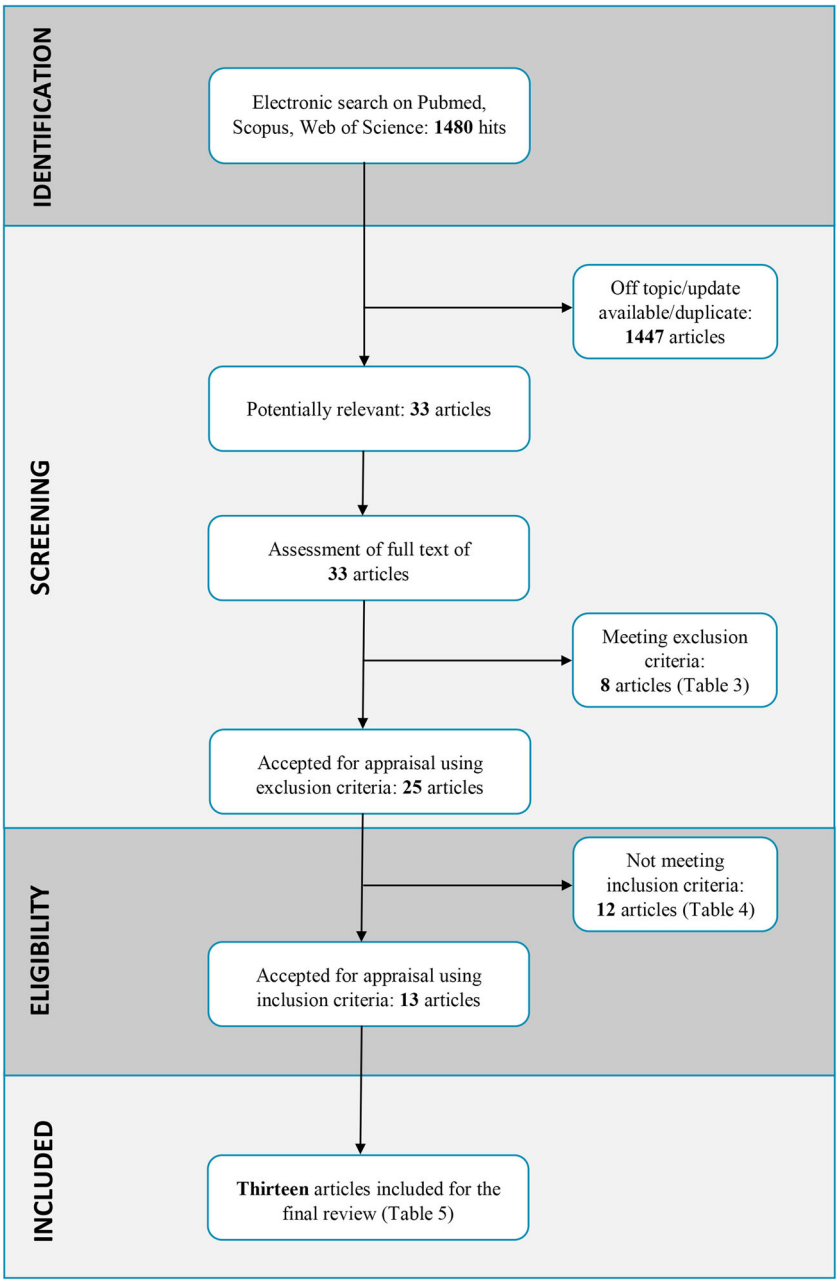

Fig. 5 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

chi-square test. Further evaluations were performed for the same parameters, using the same test, dividing the patients on the basis of primary disease, reasons of ONJ, and medications causing MRONJ.

A p value < 0.05 was considered statistically significant for all tests.

Methodological quality assessment

Quality assessment of non-randomized studies including case-control and prospective and retrospective cohort studies was performed according to the Newcastle-Ottawa Scale (NOS). Based on a system assigning a rank of one to nine stars, the NOS was developed to provide a simple tool for quality assessment of non-randomized studies included in a systematic review.

Results

Flow diagram resuming screening process is represented in Fig. 5. From an original yield of 1480 titles and 143 abstracts, 33 studies were selected for full-text analysis.

A first screening was performed through elimination of eight studies [22–29] that met the exclusion criteria (Table 2). Then, eligibility of the remaining 25 studies was evaluated, discarding 12 studies [30–41] that did not meet the inclusion criteria (Table 3).

This led to a final selection of 13 studies [42–54]. Among these, three studies had parts which had to be excluded as they did not meet inclusion criteria or met the exclusion criteria: one [43] had a part which treated unconventional therapies; one [50] had a part in which outcomes were not evaluated according to stage at diagnosis; one [51] had a part in which treatment outcome was evaluated on

Table 2 Articles discarded meeting exclusion criteria

Year	Author	Title	Study type	Reason for exclusion
2007	Petrucci et al. [22]	"Role of ozone therapy in the treatment of osteonecrosis of the jaws in multiple myeloma patients"	Letter to the Editor	Absence of original clinical study Unconventional treatment
2008	Bocanegra-Pèrez et al. [23]	"Bisphosphonate-associated osteonecrosis of the jaw. A proposal for conservative treatment"	Case series	Absence of original clinical study
2012	Agrillo et al. [24]	"Bisphosphonate-related osteonecrosis of the jaw (BRONJ) 5 year experience in the treatment of 131 cases with ozone therapy"	Retrospective	Unconventional treatment
2013	Otto et al. [25]	"Successful surgical management of osteonecrosis of the jaw due to RANK-ligand inhibitor treatment using fluorescence guided bone resection"	Case series	Absence of original clinical study Unconventional treatment
2014	Duarte et al. [26]	"Bisphosphonate-associated osteonecrosis of the jaws: analysis of a case series at a dental school"	Retrospective	Follow-up not specified
2014	Campisi et al. [27]	"Epidemiology, clinical manifestations, risk reduction and treatment strategies of jaw osteonecrosis in cancer patients exposed to antiresorptive agents"	Review	Absence of original clinical study
2014	Altay et al. [28]	"Low-level laser therapy supported surgical treatment of bisphosphonate related osteonecrosis of jaws: a retrospective analysis of 11 cases"	Prospective	Unconventional treatment
2015	Ruggiero et al. [29]	"Disease Stage and Mode Of Therapy Are Important Determinants of Treatment Outcomes for Medication-Related Osteonecrosis of the Jaw"	Retrospective	"Complete healing" outcome data mixed with "improvement" outcome data

Table 3 Articles discarded not meeting inclusion criteria

Year	Author	Title	Study type	Reason for exclusion
2007	Yarom et al. [30]	"Osteonecrosis of the jaw induced by orally administered bisphosphonates: incidence, clinical features, predisposing factors and treatment outcome"	Retrospective	Unclear therapeutic approach (lack of details of both surgical and medical approaches)
2007	Rincón et al. [31]	"Osteonecrosis of the jaws and bisphosphonates. Report of fifteen cases. Therapeutic recommendations"	Retrospective	Lesions not staged according to AAOMS MRONJ classification
2008	Van den Wyngaert et al. [32]	"Initial experience with conservative treatment in cancer patients with osteonecrosis of the jaw (ONJ) and predictors of outcome"	Retrospective	Unclear therapeutic approach (lack of details of surgical approach)
2008	Ibrahim et al. [33]	"Osteonecrosis of the Jaw in Patients with Bone Metastases Treated with Bisphosphonates: A Retrospective Study"	Retrospective	Lesions not staged according to AAOMS MRONJ classification
2010	Williamson et al. [34]	"Surgical management of bisphosphonate induced osteonecrosis of the jaws"	Prospective	Lesions not staged according to AAOMS MRONJ classification
2010	Scoletta et al. [35]	"Treatment outcomes in patients with bisphosphonate-related osteonecrosis of the jaws: a prospective study"	Prospective	Lesions not staged according to AAOMS MRONJ classification
2010	Vescovi et al. [36]	"Surgical approach with Er:YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT)"	Retrospective	Information about medication that caused MRONJ not provided
2011	Moretti et al. [37]	"A prospective clinical trial for assessing the efficacy of a minimally invasive protocol in patients with bisphosphonate-associated osteonecrosis of the jaws"	Prospective	Lesions not staged according to AAOMS MRONJ classification
2011	Eckardt et al. [38]	"Surgical Management of Bisphosphonate-related Osteonecrosis of the Jaw in Oncologic Patients - A Challenging Problem"	Retrospective	Lesions not staged according to AAOMS MRONJ classification
2014	Vescovi et al. [39]	"Conservative Surgical Management of Stage I Bisphosphonate-Related Osteonecrosis of the Jaw"	Retrospective	Lesions not staged according to AAOMS MRONJ classification
2015	Fukushima et al. [40]	"Usability of surgical treatment in cases of bisphosphonate-related osteonecrosis of the jaw stage 2 with sequestrum"	Retrospective	Information about medication that caused MRONJ not provided
2015	Bodem et al. [41]	"Value of nonsurgical therapeutic management of stage I bisphosphonate-related osteonecrosis of the jaw"	Prospective	Medical treatment that caused MRONJ not concluded at the time of the study

one case only (and was thus considered the same way as case reports).

Study characteristics

Descriptive data related to the included 13 studies are reported in Table 4. None of the studies was case-controlled or randomized. Nine studies had a retrospective design [42–46, 48, 50, 53, 54] and four were prospective studies [47, 49, 51, 52]; one was single-blinded [45], whereas for the other 12, these data were not available. Five studies were conducted in private practice [46, 50, 51, 53, 54], whereas five studies were performed in a university setting [43, 44, 47–49]. Only one study was conducted both in private practice and in university [45]. Outcomes of other two studies were not reported [42, 52].

Table 4 Characteristics of included studies

Year	Author	Title	Study type	Clinical intervention	Follow-up (months)
2011	Wilde et al. [42]	"The role of surgical therapy in the management of intravenous bisphosphonates-related osteonecrosis of the jaw"	Retrospective	Surgery (marginal or segmental resection) with per OS antimicrobics (amoxicillin + sulbactam or penicillin + metronidazole/clindamycin) and antiseptics (oral rinse with peroxide 1–3%)	3–42
2011	Atalay et al. [43]	"Bisphosphonate-related osteonecrosis: laser-assisted surgical treatment or conventional surgery?"	Retrospective	Surgery (debridement) with per OS amoxicillin (875 mg) + clavulanic ac. (125 mg) + metronidazole (500 mg) 2/day, oral rinse with chlorhexidine 0.2% 2/day	3–18
2012	Voss et al. [44]	"Surgical treatment of bisphosphonate-associated osteonecrosis of the jaw: Technical report and follow up of 21 patients"	Retrospective	Surgery (marginal resection) with EV penicillin (6 g/daily) or per OS clindamycin (600 mg) 3/day + (in case of purulent infection) metronidazole (500 mg) 2/day	24
2012	Jabbour et al. [45]	"The outcomes of conservative and surgical treatment of stage 2 bisphosphonate-related osteonecrosis of the jaws: a case series"	Retrospective	G_1: amoxicillin + clavulanic acid/penicillin VK+ oral rinse with chlorhexidine 0.12% 2/day (conservative) G_2: Surgery (debridement or resection) with amoxicillin + clavulanic acid + oral rinse with chlorhexidine 0.12% 2/day	6–17
2012	Ferlito et al. [46]	"Treatment of bisphosphonate-related osteonecrosis of the jaws: presentation of a protocol and an observational longitudinal study of an Italian series of cases"	Retrospective	Surgery (debridement) with IM piperacillin/tazobactam (2 g) 2/day for 5 days, then EV imipenem/cilastatin (500 mg) 2/day for 5 days, then piperacillin/tazobactam (2 g) 2/day for 7 days + oral rinse with chlorhexidine 0.12 or iodopovidone 10%	6
2012	Bocanegra-Pèrez et al. [47]	"Use of platelet-rich plasma in the treatment of bisphosphonate related osteonecrosis of the jaw"	Prospective	Surgery (debridement) + L-PRP with per OS amoxicillin (875 mg) + clavulanic ac. (125 mg) 3/day for 7–10 days + oral rinse with chlorhexidine 0.12%	1–3.5
2013	Mozzati et al. [48]	"A report on a 7-year Follow up of the Surgical Management with PRGF-ENDORET® of Oncologic Patients Affected by Intravenous Bisphosphonate Related Osteonecrosis of the Jaw"	Retrospective	Surgery (marginal resection) + PRGF with per OS amoxicillin + clavulanic ac. 3/day for 10 days	84
2014	Kim et al. [49]	"Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study"	Prospective	Surgery (marginal resection) + L-PRF with EV III generation cephalosporin (1 g) 2/day + oral rinse with chlorhexidine 0.12%	6
2014	Longo et al. [50]	"Platelet rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw: personal experience and review of the literature"	Retrospective	Conservative per OS ciprofloxacin (500 mg) + oral rinse 2/day for 2/4 weeks with chlorhexidine 0.2% (4 weeks)	6–94
2015	Rugani et al. [51]	"Stage-related treatment concept of medication-related osteonecrosis of the jaw - a case series"	Prospective	Stage I: amoxicillin + clavulanic acid, oral mouth rinse with antiseptic fluids, coverage of exposed bone with an adhesive paste Stage II: surgery (debridement) with amoxicillin + clavulanic acid, oral mouth rinse with antiseptic fluids Stage III: resective surgery	12
2015	Reich et al. [52]	"Surgical treatment of bisphosphonate-associated osteonecrosis: Prognostic score and long-term results"	Prospective	Surgery (marginal or segmental) with moxifloxacin or clindamycin or amoxicillin + clavulanic acid or cefuroxim or amoxicillin + clavulanic acid + metronidazole with antiseptic mouth rinse	16.5–37.8
2015	Lopes et al. [53]	"Surgical therapy for Bisphosphonate-Related Osteonecrosis of the Jaw: Six Year Experience of a Single Institution"	Retrospective	Surgery (marginal or segmental resection) with per OS clindamycin or amoxicillin + metronidazole or amoxicillin	10
2016	Bodem et al. [54]	"Surgical management of bisphosphonate-related osteonecrosis of the jaw stages II and III"	Retrospective	Surgery (marginal resection) with EV ampicillin-sulbactam (1.5 g) 3/day for 6 days or per OS clindamycin (600 mg) 3/day for 7 days with antiseptic mouth rinse (chlorhexidine 0.12%) 3/day	3

Table 5 Newcastle-Ottawa Quality Assessment Scale for cohort studies

Author	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts
Wilde et al. [42]	N	N	A	A	I	A	A	A
Atalay et al. [43]	I	A	A	A	A	A	A	A
Voss et al. [44]	I	N	A	A	I	A	A	A
Jabbour et al. [45]	I	A	A	A	A	A	A	A
Ferlito et al. [46]	A	N	A	A	A	A	A	A
Bocanegra-Pèrez et al. [47]	I	N	A	A	I	A	A	A
Mozzati et al. [48]	I	N	A	A	A	A	A	A
Kim et al. [49]	I	N	A	A	A	A	A	A
Longo et al. [50]	A	N	A	A	A	A	A	A
Rugani et al. [51]	A	N	A	A	I	A	A	A
Reich et al. [52]	N	N	A	A	I	A	A	I
Lopes et al. [53]	A	N	A	A	I	A	A	A
Bodem et al. [54]	A	N	A	A	A	A	A	A

The therapeutic pathways proposed in the papers were either conservative [45, 50, 51] or surgical [42–49, 51–54]. Conservative treatments consisted of antibiotics and antiseptics administered even for long periods; in Table 4, dosage/duration of conservative treatment is not specified if not provided in the study.

Surgical treatments consisted in complete removal of the necrotic bone, resecting until "normally bleeding bone" was reached, and were performed in every study in association with previous and consecutive (peri-operative) antimicrobial/antiseptic therapy. This led to different approaches, ranging from sole debridement to marginal resection and segmental resection.

Thus, four different types of clinical intervention were evaluated: in five studies, marginal or segmental resection with per OS/EV antimicrobics and per OS antiseptics was analyzed [42, 44, 52–54]; in two studies, debridement with per OS/IM/EV antimicrobics and per OS antiseptics was performed [43, 46], while three studies were conducted using platelet-based adjuvants [47–49].

In one study, clinical intervention changed in relation to ONJ staging [51] and in another one, the first group (G_1) was treated with conservative approach and the second (G_2) with surgery [45]. Conservative therapy was tested in only one study [50].

The follow-up periods varied both within but also between the studies (i.e., from 1 to 3.5 months [47], 3 months [54], from 3 to 18 months [43], from 3 to 42 months [42], 6 months [46, 49], from 6 to 17 months [45], from 6 to 94 months [50], 12 months [51], 10 months [53], from 16.5 to 37.8 months [52], 24 months [44], and 84 months [48]).

Quality assessment of 13 included articles was evaluated following "Newcastle-Ottawa Quality Assessment Scale for cohort studies" and reported in Table 5.

Patient's characteristics

Patient's data are resumed in Table 6. The studies reported a total of 582 patients (159 males and 423 females) with an age range between 39 and 81 years. Primary diseases that required the use of anti-angiogenic and/or anti-resorptive drugs were breast carcinoma (40.3%), osteoporosis (20.4%), multiple myeloma (14.1%), prostate carcinoma (11.1%), and other tumors (14.1%). Only two papers did not report or specify the primary disease [46, 54].

Medications that caused MRONJ comprised bisphosphonates [42, 54], anti-angiogenic [51], and anti-resorptive [51, 52] drugs, used alone or in combination. These were zolendronate alone (67.7%) or in combination (5.1%), alendronate (11.8%), pamidronate (7.3%), ibandronate (3.7%), risedronate (2.9%), and other drugs/combinations (1.5%).

Twenty dropouts were reported in three studies [46, 51, 52], whereas drug-holiday was applied in seven papers [42–46, 53, 54].

Medication-related osteonecrosis of the jaws characteristics

MRONJ details (sites, location, staging, reasons), healing outcome, and adverse events are summarized in Tables 7 and 8.

Table 6 Patient's characteristics

Author	Number of patients*	Gender (M/F)	Mean age of patients (years)	Range age of patients (years)	Primary disease	Medication causing MRONJ*	Dropout (Y/N)	Drug-holiday (Y/N)**
Wilde et al. [42]	24	12/12	NA	NA	• PCa (7) • BCa (6) • MM (7) • HL (1) • NHL (1) • ThCa (1) • KCa (1)	• ZOL EV (14) • ZOL EV + IBA EV (3) • ZOL EV + PAM EV (3) • ZOL EV + IBA EV + PAM EV (4)	No	Yes (10 patients)
Atalay et al. [43]	20	7/13	55.4	NA	• PCa (1) • BCa (11) • MM (7) • Neur (1)	• ZOL EV (20)	No	Yes
Voss et al. [44]	21	5/16	68.5	NA	• PCa (2) • BCa (9) • Plasm (3) • VuCa (1) • KCa (2) • Op (4)	• ZOL EV (14) • IBA OS (2) • ALE OS (4) • PAM EV + ZOL EV + ALE OS (1)	No	Yes
Jabbour et al. [45]	G_1: 8 G_2: 6	4/10	69.07	69.07 ± 10.37	• PCa (2) • BCa (5) • KCa (2) • MM (1) • Op (4)	• ZOL EV (7) • ALE OS (4) • PAM EV (3)	No	Yes (9 patients)
Ferlito et al. [46]	94	30/64	66	66 ± 11	NA	• ZOL EV (69) • ALE OS (16) • NER EV or IM (4) • IBA EV (1) • CLO IM (1)	Yes (3 patients)	Yes
Bocanegra-Pèrez et al. [47]	8	2/6	66	NA	• BCa (2) • MM (4) • Op (2)	• ZOL EV (3) • ALE OS (2) • ZOL EV + PAM EV (2) • PAM + CLO (1)	No	No
Mozzati et al. [48]	32	10/22	69.7	NA	• PCa (6) • BCa (5) • LCa (4) • MM (14) • OvCa (3)	• ZOL EV (26) • PAM EV (6)	No	No
Kim et al. [49]	34	0/34	71	NA	• Op (32) • BM (2)	• ZOL EV (3) • ALE OS (19) • PAM EV (4) • RIS OS (8)	No	No
Longo et al. [50]	72	12/60	59	37–81	• PCa (9) • BCa (54) • MM (1) • LCa (8)	• ZOL EV (48) • PAM EV (22) • ALE OS (2)	No	No
Rugani et al. [51]	111	12/99	63	62 ± 10.8	• PCa (4) • BCa (46) • MM (9) • Op (43) • Others (9)	• ZOL EV (57) • IBA EV (15) • ALE OS (15) • RIS OS (9) • PAM EV (1) • ALE OS + IBA EV (3) • ZOL EV + IBA EV (2) • ALE OS + ZOL EV (1) • ZOL EV + PAM EV (1) • ALE OS + PAM EV (1)	Yes (4 patients)	No

Table 6 (continued)

Author	Number of patients*	Gender (M/F)	Mean age of patients (years)	Range age of patients (years)	Primary disease	Medication causing MRONJ*	Dropout (Y/N)	Drug-holiday (Y/N)**
						• ALE OS + DEN SC (1) • ZOL EV + SUN OS (1) • ZOL EV + THA OS (1) • IBA EV + PAM EV + ZOL EV (1) • RIS OS + ALE OS + ZOL EV (1) • ZOL EV + BEV EV (1)		
Reich et al. [52]	80	40/40	69.4	NA	• PCa (15) • BCa (25) • MM (16) • KCa (9) • Op (5) • HL (1) • Others (9)	• ZOL EV (64) • IBA OS (4) • ALE OS (5) • PAM EV (4) • ZOL EV + IBA OS (1) • ZOL EV + DEN SC (2)	Yes (13 patients)	No
Lopes et al. [53]	33	8/25	65.6	39–83	• PCa (4) • BCa (18) • MM (4) • LCa (4) • KCa (1) • Op (2)	• ZOL EV (22) • PAM EV (3) • ZOL EV + PAM EV (5) • ALE OS (2) • ALE OS + ZOL EV (1)	No	Yes (31 patients)
Bodem et al. [54]	39	17/30 (sites)	71	72 ± 9	• Malignant disease (47)	• ZOL EV (47)	No	Yes (15 patients)

NA not available, *MM* multiple myeloma, *BCa* breast cancer, *PCa* prostate cancer, *ThCa* thyroid cancer, *KCa* kidney cancer, *HL* Hodgkin's lymphoma, *NHL* non-Hodgkin's lymphoma, *Neur* neuroendocrine tumor, *Plasm* plasmocytoma, *VuCa* vulval carcinoma, *Op* osteoporosis, *LCa* lung carcinoma, *OvCa* ovarian carcinoma, *BM* bony metastases, *OS* orally, *EV* endovenous, *IM* intramuscular, *SC* subcutaneous, *G* group, *ZOL* zolendronate, *PAM* pamidronate, *IBA* ibandronate, *ALE* alendronate, *NER* neridronate, *CLO* clodronate, *RIS* risedronate, *DEN* denosumab, *SUN* sunitinib, *THA* thalidomide, *BEV* bevacizumab

*"Number of patients" and "Medication causing MRONJ" sections refer to the whole study

**"Drug-holiday" is not dictated by the presence of ONJ, but the condition of each patient

The studies reported a total of 619 ONJ sites with different staging: at risk (11.6%), stage 0 (1.3%), stage I (7.6%), stage II (59%), and stage III (20.6%). Location of osteonecrosis was in the mandible in 68.8% of cases, maxilla/upper jaw in 27.6%, and both (mandible and maxilla) in 3.6%. In only two studies, the data about ONJ location was not available [46, 50].

The potential causes associated with the development of ONJ were tooth extraction (47.6%), prosthetic trauma (21.4%), periodontal disease (10.6%), dental implant placement (2.8%), and other (6.2%), whereas were also reported spontaneous cases (7.6%) and reasons unknown (3.8%). In three studies, the potential causes were not reported [46, 51, 54].

All studies reported the results of therapies (complete healing, partial healing, no healing) in terms of percentage of success. In five cases [43, 45, 46, 51, 52], the outcomes according to AAOMS staging were recalculated with data provided by the authors in the papers.

Adverse events

Adverse events are presented in Tables 7 and 8. In three studies, flap dehiscence was noted [42, 51, 53], whereas recurrence of osteonecrosis was observed in two studies [42, 44]. Fistula and suppuration were reported in three articles [44, 49, 51], severe pain in one study [46], progression of ONJ in one study [52], new ONJ site in one study [48], and pathologic fracture of the mandible in one study [53]. In the remaining studies, these data were not reported [43, 45, 47, 50, 54].

Statistical analysis

Proceeding from the 13 selected studies, 618 sites with ONJ were enrolled in this statistical analysis, 385 in the non-drug-holiday group, and 233 in the drug-holiday group. Cumulative percentage of healed sites at follow-up was 67.2% (56.4% in

Table 7 Drug-holiday studies

Author	ONJ sites	ONJ location	ONJ staging	Reasons of ONJ	Complete healing	Partial healing	No healing	Adverse events
Wilde et al. [42]	33	• Mnd (20) • Max (13)	• 6 (I) • 12 (II) • 15 (III)	• Tooth extraction (19) • Prosthesis (10) • Incision after abscess (1) • Periodontal disease (2) • Reason unknown (1)	• Stage I: 100% • Stage II: 100% • Stage III: 73.3%	• Stage I: 0% • Stage II: 0% • Stage III: 0%	• Stage I: 0% • Stage II: 0% • Stage III: 26.-7%	• Early flap dehiscence (3 patients, stage III) • Recurrence (1 patient, stage III)
Atalay et al. [43]	20	• Mnd (9) • Max (11)	• 6 (I) • 14 (II)	• Minor oral surgery (20)	• Stage I: 0% • Stage II: 80%	• Stage I: 100-% • Stage II: 20%	• Stage I: 0% • Stage II: 0%	NA
Voss et al. [44]	21	• Mnd (16) • Max (3) • Both (2)	• 16 (II) • 5 (III)	• Tooth extraction (14) • Reason unknown (7)	• Stage II: 87.5% • Stage III: 100%	• Stage II: 0% • Stage III: 0%	• Stage II: 12.-5% • Stage III: 0%	• Fistula (1 patient, stage II) • Recurrence (1 patient, stage II)
Jabbour et al. [45]	G_1: 11 G_2: 8	• Mnd (15) • Max (4)	• 19 (II)	• Tooth extraction (8) • Prosthesis (4) • Spontaneous (1) • Reason unknown (1)	• G_1: 63.6% • G_2: 62.5%	• G_1: 18.-2% • G_2: 12.-5%	• G_1: 18.-2% • G_2: 25%	NA
Ferlito et al. [46]	94	NA	• 8 (I) • 86 (II)	NA	• Stage I: 100% • Stage II: 91.4%	• Stage I: 0% • Stage II: 0%	• Stage I: 0% • Stage II: 8.6-%	• Severe pain (3 patients, stage II)
Lopes et al. [53]	46	• Mnd (24) • Max (21) • Both (1)	• 37 (II) • 9 (III)	• Tooth extraction: (16) • Dental implant (3) • Periodontal disease: (9) • Prosthesis: (8) • Spontaneo-us: (8) • Palatal tori (2)	• Stage II: 89% • Stage III: 78%	• Stage II: 5.5-% • Stage III: 11%	• Stage II: 5.5-% • Stage III: 11%	• Pathologic fracture of the mandible (1 patient, stage II) • Early flap dehiscence (6 patients, stage II, III)

Table 7 (continued)

Author	ONJ sites	ONJ location	ONJ staging	Reasons of ONJ	Complete healing	Partial healing	No healing	Adverse events
Bodem et al. [54]	47	• Mnd (34) • Max (13)	• 23 (II) • 24 (III)	NA	• Stage II: 52.2% • Stage III: 50%	• Stage II: 30.-4% • Stage III: 29.-2%	• Stage II: 17.-4% • Stage III: 20.-8%	NA

NA not available, *Mnd* mandible, *Max* maxilla, *I* ONJ stage I, *II* ONJ stage II, *III* ONJ stage III

non-drug-holiday group and 85% in drug-holiday group), showing a significantly higher prevalence of completely healed sites in patients who followed the drug-holiday protocol (Table 9).

No statistically significant differences were found when comparing the effects of reasons of ONJ, except for the "spontaneous" group, where drug-holiday patients experienced a higher prevalence of completely healed sites (Table 10).

No statistically significant differences were reported when comparing the effects of primary disease requiring anti-angiogenic/anti-resorptive treatment, except for "multiple myeloma" and "osteoporosis" group, where drug-holiday patients experienced a higher prevalence of completely healed sites (Table 11).

Finally, patients undergoing treatment with alendronate, ibandronate, and zolendronate showed higher rates of complete healing when treated with drug-holiday protocols.

Discussion

Currently, the management of patients affected by medication-related osteonecrosis of the jaws is based on individual protocols, which emerged from clinical experience, since there are no definitive treatment guidelines. Stage-specific therapy concept has reached consensus [10] among clinicians who are making efforts to find the best treatment for this disease. It appears that different approaches may lead to better results when applied at a certain stage of the disease.

The present systematic review has evaluated the efficacy of stage-specific therapies in patients affected by medication-related osteonecrosis of the jaws and, more in general, if stage-specific approach has its rationale, which may lead to craft definitive treatment guidelines.

All studies included in our review defined full recovery as mucosal healing, bone coverage, symptom regression, and disappearing of radiographic signs, and they all reported of necessity of peri-operative pain control, gained with NSAD/opioids, even at high doses. However, all studies selected were neither case-controlled nor randomized and with a small-sized sample, thus giving a low-grade of scientific evidence to the actual knowledge on MRONJ therapy.

Literature analysis shows that medical therapy has different success rates, lower and more heterogeneous in advanced stages (100% stage 0, stage I range 81–97%, stage II range 63.6–100%, stage III 73%), while surgical therapy shows very heterogeneous results at every stage (stage I range 0–100%, stage II range 52–100%, stage III range 50–100%).

According to results of the present systematic review, it can be recommended to start MRONJ treatment with a first period of conservative treatment for 2 weeks, since this approach has shown effectiveness at all stages (even if differences in the success rate were found). A conservative approach appears to bear clinical relevance since it may avoid unnecessary surgical treatment, which is extremely important when considering all related risks. Furthermore, even if conservative treatment does not lead to a complete resolution of the problem, it may improve the ONJ wound, possibly leading to a less invasive surgery. A surgical approach can still be adopted in patients who are refractory to conservative treatment [55]. Moreover, the duration of conservative treatment can be continued for months, until either full recovery or substantial improvement is reached. Interestingly, it has to be pointed out that despite the fact that a wide range of antibiotics has been suggested in combination with different antiseptic mouth rinses (Table 4), the dosage of antibiotics/antiseptics was not specified in every paper.

On one hand, it appears clear that only case-controlled study would give certainty on the effectiveness of conservative treatment, especially in cases of advanced MRONJ stages (e.g., II and III), in which the success rates and the pharmacological approach are more heterogeneous.

On the other hand, until data from case-controlled studies are not available, literature analysis suggests that treatment of MRONJ stages 0 and I should consist essentially of a conservative approach, both because of the high success rates obtained in these cases (even if these findings are based on case series) may give a certain confidence and because of the less heterogeneous results compared to those obtained with a surgical approach at these early stages (i.e., range 0–100% in

Table 8 Non-drug-holiday studies

Author	ONJ sites	ONJ location	ONJ staging	Reasons of ONJ	Complete healing	Partial healing	No healing	Adverse events
Bocanegra-Pèrez et al. [47]	8	• Mnd (7) • Max (1)	• 8 (II)	• Tooth extraction (5) • Prosthesis (1) • Reason unknown (2)	• Stage II: 100%	• Stage II: 0%	• Stage II: 0%	NA
Mozzati et al. [48]	32	• Mnd (24) • Max (8)	• 32 (II)	• Tooth extraction (17) • Prosthesis (7) • Periodontal disease (8)	• Stage II: 100%	• Stage II: 0%	• Stage II: 0%	• New ONJ in other sites (5 patients, stage II)
Kim et al. [49]	34	• Mnd (27) • Max (7)	• 7 (I) • 21 (II) • 6 (III)	• Tooth extraction (23) • Dental implant (4) • Prosthesis (2) • Spontaneous (5)	• Stage I: 100% • Stage II: 85.7% • Stage III: 16.6%	• Stage I: 0% • Stage II: 14.3% • Stage III: 50%	• Stage I: 0% • Stage II: 0% • Stage III: 33.4%	• Suppurative discharge (2 patients, stage III)
Longo et al. [50]	72	NA	• 5 (0) • 11 (I) • 41 (II) • 15 (III)	• Tooth extraction (47) • Prosthetic trauma (3) • Periodontal disease (15)	• Stage 0: 100% • Stage I: 81% • Stage II: 76% • Stage III: 73%	• Stage 0: 0% • Stage I: 9% • Stage II: 24% • Stage III: 27%	• Stage 0: 0% • Stage I: 0% • Stage II: 0% • Stage III: 0%	NA
Rugani et al. [51]	113	• Mnd (16) • Max (7) (patients underwent surgery)	• 72 (risk) • 3 (0) • 6 (I) • 25 (II) • 7 (III)	NA	• Stage I: 97% • Stage II—surgical debridement: 88.2% • Stage II—conservative therapy: 100% • Stage III: 100%	• Stage I: 3% • Stage II—surgical debridement: 0% • Stage II—conservative therapy: 0% • Stage III: 0%	• Stage I: 0% • Stage II—surgical debridement: 11.8% • Stage II—conservative therapy: 0% • Stage III: 0%	• Early flap dehiscence (1 patient, stage II) • Fistula (1 patient, stage II)
Reich et al. [52]	80	• Mnd (58) • Max (12) • Both (10)	• 3 (I) • 31 (II) • 33 (III)	• Tooth extraction (27) • Prosthesis (22) • Spontaneous (12) • Periodontal disease (5) • Dental implant (3) • Other (11)	• Stage I: 100% • Stage II: 58% • Stage III: 42.5%	• Stage I: 0% • Stage II: 25.8% • Stage III: 39.5%	• Stage I: 0% • Stage II: 16.2% • Stage III: 18%	• Progression of ONJ (1 patient, stage II)

NA not available, *Mnd* mandible, *Max* maxilla, *I* ONJ stage I, *II* ONJ stage II, *III* ONJ stage III

Table 9 Cumulative percentage of healed sites at follow-up between drug-holiday and non-drug-holiday groups

Drug-holiday	Author	ONJ sites	ONJ staging	Complete healing	Incomplete healing		Adverse events	
					Partial	No		
Yes	Wilde et al. [42]	33	6 (I)	100	0	0	No	0.057
			12 (II)	100	0	0	No	
			15 (III)	73.3	0	26.7	Early suture dehiscence (3) Recurrence (1)	
	Atalay et al. [43]	20	6 (I)	0	100	0	NA	
			14 (II)	80	20	0	NA	
	Voss et al. [44]	21	16 (II)	87.5	0	12.5	Fistula (1) Recurrence (1)	
			5 (III)	100	0	0	No	
	Jabbour et al. [45]	11 G_1	11 (II)	63.6	18.2	18.2	NA	
		8 G_2	8 (II)	62.5	12.5	12.5	NA	
	Ferlito et al. [46]	94	8 (I)	100	0	0	No	
			86 (II)	91.4	0	8.6	Severe pain (3)	
	Lopes et al. [53]	46	37 (II)	89	5.5	5.5	Pathologic fracture of the mandible (1) Wound dehiscence (4)	
			9 (III)	78	11	11	Wound dehiscence (2)	
	Bodem et al. [54]	47	23 (II)	52.2	30.4	17.4	NA	
			24 (III)	50	29.2	20.8	NA	
No	Bocanegra-Pèrez et al. [47]	8	8 (II)	100	0	0	NA	0.0001
	Mozzati et al. [48]	32	31 (II)	100	0	0	New ONJ in other sites (5)	
	Kim et al. [49]	34	7 (I)	100	0	0	Suppurative discharge (2)	
			21 (II)	85.7	14.3	0		
			6 (III)	16.6	50	33.4		
	Longo et al. [50]	72	5 (0)	100	0	0		
			11 (I)	81	9	0		
			41 (II)	76	24	0		
			15 (III)	73	27	0		
	Rugani et al. [51]	113	6 (I)	97	3	0		
			25(II)	88.2 (surgery)	0	11.8	Early suture dehiscence (1)	
				100 (conservative)	0	0		
			7(III)	100	0	0	Fistula (1)	
	Reich et al. [52]	80	3 (I)	100	0	0		
			31 (II)	58	25.8	16.2	Progression of ONJ (1)	
			33 (III)	42.5	39.5	18		
	Fisher's exact test 0.0001							

stage I). Furthermore, stage 0 cases have shown complete response to medical therapy, but the sample size is very small (i.e., five patients).

A surgical approach with marginal or segmental resection of necrotic bone or tissue debridement [55] may be performed at all stages, but with heterogeneous results (stage I range 0–100%, stage II range 52–100%, stage III range 50–100%). The results of the present literature analysis indicate the choice among debridement, marginal, or segmental resection is linked to the "normally bleeding bone" principle (which means removing necrotic tissue until normal bone appears and performing first intention wound closing) and thus to the site/extent of osteonecrosis lesions. However, it needs to be pointed out that surgery was performed in every case with concomitant antimicrobial/antiseptic therapy and without any control group undergoing either conservative therapy or

Table 10 Effects of reasons of ONJ on healing between drug-holiday and non-drug-holiday groups

Reasons of ONJ	Number	Drug holiday	Incomplete healing (*n*)	Complete healing (*n*)	Significance
Dental implant	10	N	5	2	0.167
		Y	0	3	
Incision after abscess	1	N	0	0	NA
		Y	0	1	
Minor oral surgery	20	N	0	0	NA
		Y	9	11	
Other	11	N	11	0	NA
		Y	0	0	
Palatal tori	2	N	0	0	NA
		Y	1	1	
Periodontal disease	46	N	16	19	0.320
		Y	3	8	
Prosthesis	54	N	8	24	0.742
		Y	4	18	
Prosthetic trauma	3	N	3	0	NA
		Y	0	0	
Reason unknown	11	N	0	2	0.999
		Y	3	6	
Spontaneous	26	N	12	5	0.038
		Y	2	7	
Tooth extraction	177	N	8	111	0.501
		Y	2	56	
NA	253	N	105	54	0.001
		Y	7	87	
Missing data	4	N	0	0	NA
		Y	3	1	

NA not available

placebo. In turn, this limits the evidence on the effectiveness of surgical therapy since it cannot be excluded that healing may have been reached through antimicrobial/antiseptic therapy.

Although the statistical analysis indicates that drug-holiday group shows a higher prevalence of completely healed sites compared to non-drug-holiday group (as well as higher rates of complete healing for cases of "multiple myeloma" and "osteoporosis" and for patients undergoing treatment with alendronate, ibandronate, and zolendronate), from a clinician's point of view, it can be suggested that this protocol should not be dictated by the presence of osteonecrosis, but by the condition of each patient. This is in agreement with previous suggestions [42, 45, 53, 54], especially when patients have taken bisphosphonates (these drugs form an irreversible bond with the bone hydroxyapatite crystals that give bone half-life of about 11 years [56]). Moreover, since the suspension will not decrease the pharmacological effect on bone metabolism, the discontinuation of the drugs could increase the risk of skeletal complications, recurrences of pain, progression of osteolytic lesions, or bony metastases [46, 48].

Platelet-based adjuvants (L-PRP, L-PRF, PRGF) have been proposed to improve surgery outcome. However, at present, no randomized case-controlled studies have proved their efficacy in MRONJ therapy. On the other hand, some studies (i.e., based on small samples and no controls) have reported good outcomes (L-PRP: 100% stage II; PRGF: 100% stage II; L-PRF: 100% stage I, 85% stage II, 16.6% stage III) [47–49]. Therefore, the present literature analysis suggests that platelet-based adjuvant may be worthwhile to be further investigated in order to understand if they may have a role both on the acceleration of the healing process and improvement of success rates.

Finally, stage-specific evaluation of success of different MRONJ therapeutic pathways seems a valid approach and has shown its rationale in the present analysis. Conservative therapy, which is less operator-dependent than surgery and therefore more easily assessable in the context of a systematic review, has demonstrated the best and less heterogeneous results at early stages (i.e., stage 0: 100%; stage I: range 81–97% vs. range 0–100%). Advanced stages show similarly heterogeneous results (conservative therapy stage II range 63.6–100% vs. surgery stage II range 52–100%; conservative therapy stage III 73 vs. surgery stage III range 50–100%), possibly because the effectiveness of conservative therapy decreases while that of surgery increases. However, it cannot be ruled

Table 11 Effects of primary disease on healing between drug-holiday and non-drug-holiday groups

Primary disease	Number	Drug-holiday (Y/N)	Incomplete healing (*n*)	Complete healing (*n*)	Significance
BCa	181	N	64	77	0.103
		Y	12	28	
BM	2	N	0	2	NA
		Y	0	0	
HL	2	N	1	0	0.999
		Y	0	1	
KCa	15	N	0	9	NA
		Y	0	6	
LCa	24	N	10	10	0.114
		Y	0	4	
Malignant disease	39	N	0	11	0.158
		Y	6	22	
MM	63	N	19	21	0.007
		Y	3	20	
Neur	1	N	0	0	NA
		Y	0	1	
NHL	1	N	0	0	NA
		Y	0	1	
Op	92	N	32	48	0.050
		Y	1	11	
OvCa	3	N	0	3	NA
		Y	0	0	
PCa	42	N	10	14	0.750
		Y	6	12	
Plasm	3	N	0	0	NA
		Y	0	3	
ThCa	1	N	0	0	NA
		Y	0	1	
VuCa	1	N	0	0	NA
		Y	0	1	
Others	18	N	9	9	NA
		Y	0	0	
NA	94	N	0	0	NA
		Y	7	87	

BCa breast cancer, *BM* bony metastases, *HL* Hodgkin's lymphoma, *KCa* kidney cancer, *LCa* lung carcinoma, *MM* multiple myeloma, *Neur* neuroendocrine tumor, *NHL* non-Hodgkin's lymphoma, *Op* osteoporosis, *OvCa* ovarian carcinoma, *PCa* prostate cancer, *Plasm* plasmocytoma, *ThCa* thyroid cancer, *VuCa* vulval carcinoma, *NA* not available

out that the high heterogeneity of surgical outcomes was also influenced by operator skills.

Taking together, the present systematic review suggests that while stages 0 and I can be treated by means of a conservative approach, more advanced stages must be carefully evaluated and decision should be made for every single case. The data also indicate that there are still many open questions that need to be answered, especially regarding the development of optimal protocols for the treatment of advanced stages. Obviously, such questions can only be answered by adequately designed case-controlled randomized studies on surgery vs. medical treatment vs. placebo/"wait and see." Since advanced stages have more heterogeneous results, at present, prevention and treatment planning play the key role for the management of such cases, e.g., prior to start of anti-angiogenic/anti-resorptive treatment, a multidisciplinary approach [10], with accurate dental examination and detection of dental foci is mandatory.

Moreover, regular dental follow-up for patients with ongoing/history of anti-resorptive/anti-angiogenic therapy, with correct dental hygiene motivation and proper informed consent [10], would allow continuous primary and secondary prevention, detecting MRONJ at early stages.

Conclusion

The results of the present systematic review suggest that the current stage-specific approach for MRONJ therapy is based

on a sound clinical rationale and drug-holiday should be dictated by the condition of each patient. Conservative treatment appears to yield better outcomes at early stages, while further investigations are needed to elucidate the best protocols for the management of advanced stages. Hence, MRONJ should be primarily treated by means of a conservative approach while more advanced stages must be carefully evaluated. Individual decisions should be made for every single case even with respect to the drug-holiday protocol.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study (e.g., systematic review and meta-analysis), formal consent is not required.

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