Lack of evidence in reducing risk of MRONJ after teeth extractions with systemic antibiotics.

Lack of evidence in reducing risk of MRONJ after teeth extractions with systemic antibiotics~~: a systematic review~~

Marco Cabras,[1)] Alessio Gambino,[1)] Roberto Broccoletti,[1)] Savino Sciascia,[2)] and Paolo G. Arduino.[1)]

[1)] Department of Surgical Sciences, Oral Medicine Section, CIR-Dental School, University of Turin, Turin, Italy

[2)] Department of Clinical and Biological Sciences, Center of Research of Immunopathology and Rare Diseases-Coordinating Center of the Network for Rare Diseases of Piedmont and Aosta Valley, University of Turin, Turin, Italy

Corresponding Author:

Dr. Marco Cabras

Department of Surgical Sciences; CIR - Dental School.

School of Medicine, University of Turin.

Oral Medicine Unit, Via Nizza 230, I-10126 Turin (Italy).

Telephone: + 390116631522; Fax: +39011618639.

E-mail: cabrasmarco300@gmail.com

Abstract

A systematic review was carried out to identify if periprocedural administration of systemic antibiotics could decrease risk of medication-related osteonecrosis of the jaws (MRONJ) in patients under antiresorptive and/or biologic agents for teeth extraction. PubMed/MEDLINE and Scopus were systematically searched for case-series with more than 10 patients, retrospective/prospective studies, and trials concerning this issue. Manual searching of references from previous reviews was also pursued. Of 1,512 results, 17 studies were included, focusing on antibiotics for extraction in patients under intravenous bisphosphonates (8), oral bisphosphonates (2), oral and intravenous bisphosphonates (6), and denosumab (1), of which 12 performing dental extraction with surgical flap. With no trials found, "quality in prognosis studies" (QUIPS) tool was deployed to evaluate risk of bias. First-line treatment was 2-3 grams of oral amoxicillin in 76.4% of studies; 300-600 mg clindamycin was alternative treatment in 23.5% of studies. Treatment ranged from 3 to 20 days, being of 6-7 days in 47% of studies. No microbiologic insight was provided. A significantly higher risk of MRONJ for patients unexposed to antibiotics was provided in one retrospective study. QUIPS tool revealed moderate-high risk of bias. With empirical data from bias-carrying, heterogeneous observational studies, validity of antibiotics is yet to be established.

Keywords; osteonecrosis, MRONJ, teeth extraction, antibiotics, systematic review

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is defined as exposed bone, or bone that can be probed through an intraoral or extra oral fistula(e) in the maxillofacial region, unable to heal within 8 weeks, occurring in a patient with medical history significant for assumption of a bone-modifying agent (BMA), and unexposed to head and neck radiation [1]. Bisphosphonates (BP) were the first BMA linked to MRONJ with the first report published in 2003 [2]. Since then, other categories of drugs have been related to the onset of MRONJ, such as anti-angiogenic monoclonal antibody bevacizumab, firstly reported in 2008 [3], anti-receptor activator of nuclear factor-kappa B ligand (anti-RANKL)-agent denosumab, and tyrosine kinase receptor inhibitor sunitinib, described in 2010 and 2012, respectively [4,5], together with an ever-growing list of various antiangiogenics and biologic immunomodulators [6]. Epidemiology of MRONJ is still highly debated, with unknown incidence and prevalence within general population, and studies portraying its occurrence as either under-estimated [7] or over-estimated [8]. The most recent international consensus available in literature detailed the greatest incidence of MRONJ among oncology patients (1-15%), being instead estimated at 0.001-0-01% amid osteoporosis population [9]. Risk of developing MRONJ, especially in patients taking BPs, depends upon a series of factors, including route of administration, either per-os (PO) or intravenous (IV), potency, cumulative dose, duration of treatment, concurrent intake of corticosteroids, systemic disorders such as diabetes, and smoking [1,6,10]. As confirmed in a recent systematic review [11], the most commonly reported dental risk factor is dental extraction: relative risk of developing MRONJ after such procedure has been reported to be 16 to 50 higher among IV BPs patients, if compared to the same category of individuals not undergoing extraction, with a frequency of MRONJ rising up to 0.09-3% among osteoporotic patients [12]. Due to the increasing evidence on the key role of oral microbioma in promoting the occurrence of MRONJ, rather than inhibition of bone turnover alone, with invasion by Actinomyces playing a significant role [13], systemic antibiotics are often prescribed peri-operatively, both among IV-

BP and in PO-BP patients, whenever dental extraction can no longer be procrastinated, or conservative treatment is not pursuable. However, no proper consensus has been reached on which might be a reliable standardized antibiotic protocol, able to consistently reduce the risk of MRONJ among patients in need of tooth extractions.

Thus, aim of the present systematic review was to assess if periprocedural administration of systemic antibiotics might decrease the risk of osteonecrosis of the jaws in patients receiving antiresorptive and/or biologic agents when in need of teeth extraction, and ideally, which antibiotic treatment should be considered as the most effective.

Materials and Methods

P.I.C.O. question

From February 2020 to May 2020, a systematic search on MEDLINE and SCOPUS electronic databases was carried out, to ascertain publications eligible for inclusion in the study. The P.I.C.O. (patient, intervention, control, outcome) question [based on the preferred reporting items for systematic review and meta-analysis (PRISMA)] for this investigation was: “in populations of patients treated with antiresorptive agents undergoing tooth extraction, which antibiotic is more effective in reducing risk of MRONJ, compared to other antibiotics or placebo?”

The P.I.C.O. question was framed as follows:

- human patients treated with bisphosphonates/antiangiogenics/antiresorptive agents undergoing dental extraction (patients)
- any systemic antibiotic (intervention)
- no treatment, placebo or a different type of antibiotic (comparison)
- subsequent development of MRONJ (primary outcome).

The review was recorded under the PROSPERO registry (registration number CRD42020180061).

Search strategy

The following ten search strings were used for both MEDLINE and SCOPUS databases:

- "bisphosphonate osteonecrosis jaw ~~AND~~ and tooth extraction",
- "bisphosphonate osteonecrosis jaw ~~AND~~ and tooth extraction ~~AND~~ and antibiotics",
- "antiangiogenic ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction",
- "antiangiogenic ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction ~~AND~~ and antibiotics",

- "bevacizumab ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction",
- "bevacizumab ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction ~~AND~~ and antibiotics",
- "denosumab ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction",
- "denosumab ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction ~~AND~~ and antibiotics",
- "sunitinib ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction",
- "sunitinib ~~AND~~ and osteonecrosis ~~AND~~ and tooth extraction ~~AND~~ and antibiotics".

Selection of studies

Two reviewers (MC, and PGA) traced the titles and abstracts of the publications generated by this search strategy. Inclusion criteria were the following: descriptive studies as case-series with more than 10 human patients, observational studies (i.e., retrospective, prospective studies), and trials (i.e., controlled clinical trials, randomized controlled trials) assessing the efficacy of systemic antibiotic in reducing the onset of MRONJ after tooth extraction. Full-text articles were examined in case of studies that seemed to satisfy the aforementioned criteria, together with those providing insufficient information in the title and abstract to establish their eligibility. After this first stage of scrutiny, the articles satisfying the aforementioned criteria were included if information were also provided for the following elements: type of antiresorptive agent, its administration route, the underlying disease for which such treatment was required, and description of the systemic antibiotic preventive protocol (e.g., type of drug, daily dosage, route of administration, duration of treatment and follow-up). Exclusion criteria were the following: articles irrespective of the previously mentioned criteria, studies not conducted on human patients or published in language other than English, case-reports, letters to the editor, and expert opinion. The selection process was finished by manually searching through the bibliographic references of previous literature reviews emerged through the aforesaid search criteria, which would share a similar scope of

research to the present work. Disagreements were solved through consultation with the three co-workers (SS, AG, and RB).

Data extraction

The main characteristics extracted from each of the included article were the following: authors, date of publication, sample of patients enrolled, type of BP/antiresorptive/antiangiogenic, dose and administration route, site and number of dental extractions, type of antibiotic, dose, administration route and duration of treatment, and onset of MRONJ. Dental extraction techniques were grouped either as "dental extraction with soft tissue closure", if a surgical flap approach was pursued, or as "dental extractions with no soft tissue closure", if no surgical flap was performed.

Quality assessment

Studies were evaluated for risk of bias using the quality in prognosis studies (QUIPS) tool [14], which consists of 6 bias domains:

1. "study participation" domain, to assess the validity of patients' selection, inclusive of their baseline characteristics, and the eligibility criteria deployed by the Authors;
2. "study attrition" domain, to address the coherence between size of sample at baseline and at the end of the study, with a progressively higher risk of bias associated with a higher dropout rate;
3. "prognostic factor measurement" domain, to consider the appropriateness of definition and measurement of the prognostic factor – in the present review, the prognostic factor was represented by the antibiotic protocols, with a progressively higher risk of bias associated with lack of information concerning the type of drug, dosage, administration route, and duration of treatment;

4. “outcome measurement” domain, to evaluate the clarity and reliability of the outcome – in the present review, the outcome was the MRONJ event, with a progressively higher risk of bias in its measurement associated with further detachment from the MRONJ definition available in the latest literature guidelines;
5. “study confounding” domain, to determine the role of confounding factors that might be of disturbance between the prognostic factor and the outcome – in the present review, confounding factors were evaluated as those preoperative/intraoperative/postoperative approaches carried out together with antibiotic protocols to reduce risk of MRONJ, with a progressively higher risk of bias associated with the amount of perioperative approaches deployed;
6. “statistical analysis and reporting” domain, to assess the appropriateness of each study’s statistical analysis – in the present review, such domain was considered in light of a univariate or multivariate analysis focusing on the statistical association between antibiotics and MRONJ occurrence, with a progressively higher risk of bias associated with the absence of statistical analysis to examine the simultaneous effect of these multiple variables against MRONJ occurrence, and draw clear conclusions on the actual role of antibiotics alone against the onset of MRONJ.

Results

Study selection

The results of the literature search are presented in the PRISMA flow diagram (Fig. 1). Electronic search strategy yielded 1,512 records. After removal of 785 duplicates, 727 records remained. After title and abstract screening, 654 were excluded, since not-inherent with the purposes of the present work, whereas 47 were excluded, since published in language other than English. Finally, 26 articles were identified for full-text retrieval and analysis. Of these, 15 articles met all the aforementioned criteria, whilst 5, although inherent with the scope of this review, did not provide enough data to be considered eligible and had to be excluded.

The remaining six articles were previous systematic review of literature which seemed to share similar scope of interest to the present work, being focused on the role of dental extraction as risk factor for MRONJ [15], the broader spectrum of prevention strategies available to reduce risk of MRONJ [16,17], role of antibiotics to prevent MRONJ regardless of teeth extraction [18] or providing an insight on the various prevention strategies of MRONJ secondary to tooth extraction [19,20]. After consultation of the references detailed in each of these reviews, 4 more studies were attained, of which 2 were excluded and 2 were added to the eligible articles. Finally, 17 articles were considered eligible. No RCT was detected. In total, 9 prospective studies, 4 retrospective studies, 3 case-series with more than 10 patients, and 1 cohort study were collected. Of these, 8 focused on role of systemic antibiotics for teeth extraction in patients undergoing IV BPs [21-28], of which 6 where dental extraction was performed with soft tissue closure [22-26,28], and 2 with no soft tissue closure [21,27]; 2 on patients under treatment with PO BPs [29,30], of which 1 where dental extraction was performed with soft tissue closure [29], and 1 with no soft tissue closure [30]; 6 on a mixed sample consisting of patients administered with both IV and PO BPs [12,31-35], of which 4 where dental extraction was performed with soft tissue closure [12,31,34,35],

and 2 with no soft tissue closure [32,33]; and 1 article aimed to analyse patients treated with denosumab performing dental extraction with soft tissue closure [36].

Table 1 and Table 2 summarize the main characteristics of each of the 17 articles included in the present review, grouped both for type of BP/antiresorptive treatment and type of dental extraction technique.

Definition of MRONJ

As detailed for each study in Table 1, MRONJ was clearly or indirectly defined in accordance either to Association of Oral and Maxillofacial Surgeons (AAOMS) Position Paper of 2009 [37], or that of 2014 [1] in 12 (70.6%) studies [22-26,28-32,35,36].

Concerning the remaining 5 studies, one could be still considered in accordance to 2009 American AAOMS Position Paper, with regards to timing and bone exposure, despite lack of explicit mention to radiotherapy of head and neck as exclusion criterion [33], whereas in another article, the diagnosis of MRONJ was made despite patients being also exposed to radiotherapy of head and neck, either after extraction or after first MRONJ diagnosis [12]. Finally, in three articles, timing was different from the usual 8 weeks, being unspecified in one study [21], prolonged to 12 weeks in another [34], up to four months in one case [27].

Systemic antibiotic for teeth extraction in patients under IV BPs

Dental extraction with soft tissue closure

Ten studies assessed risk of MRONJ among patients treated with IV BPs and exposed to antibiotic prophylaxis for teeth extraction with soft tissue closure in the last eleven years. Of these, five prospective studies [23,24,26,34,35], three case-series [22,25,28], one retrospective study [12], and one cohort study

[31] were found. Table 2 and Table 3 show a summary of the perioperative antibiotic regimen, concurrent preventive protocols, and main characteristics of surgical protocol applied in each study.

Data from 466 patients are reported, with size of sample ranging widely from 23 [23] to 65 patients [24]. The most commonly prescribed antibiotic drug was amoxicillin, either alone [23,35] or combined with clavulanate potassium (CP) [22,24-26,34], as reported in 7 (70%) of 10 articles, being administered in a comprehensive sample of 307 patients with an overall consistent daily dosage of 2-3 grams daily among all studies.

Amoxicillin and CP was still the first-line treatment, although in combination with 1-1.5 gr metronidazole per day, in a cohort study of 44 patients [31].

Finally, β-lactam antibiotics other than amoxicillin were prescribed in the form of 1.5 gr of ampicillin-sulbactam, 3 times daily, in a hospital-based case series of 61 patients [28], and as daily dosage of 10 million UI of penicillin in the most recent retrospective study on 54 patients [12].

The most common route of prescription was by far oral, as reported in 8 (80%) of 10 studies [23-26,28,31,34,35] with amoxicillin + CP being prescribed intramuscularly in only one case-series of 34 patients [22] and penicillin being necessarily prescribed intravenously in the only study deploying such formulation [12]. Duration of antibiotic treatment was mostly within 7 days, as reported in 8 (80%) of 10 studies [12,22,24-26,28,31,34], starting 1-3 days before extraction and ending 3-5 days after extraction. Conversely, antibiotics were administered for more than 2 weeks in 2 (20%) of 10 articles, of which one as a 17-days protocol from 3 days before to 14 days after extraction [35], while another reported a 20-days antibiotic regimen, from 3 days before to 17 days after extraction [23]. Alternative antibiotic treatment was reported in 5 (50%) of 10 studies [12,24,26,28,31], mainly due to the possibility of an allergy to β-lactam family, with same route of administration and duration as the first-line treatment.

In detail, 300-600 mg clindamycin was proposed in two studies [12,28], just as erythromycin 600 mg [24,26], while lincomycin 500 mg was proposed in one study [31].

It is worth noticing that systemic antibiotics were never the only prophylactic protocol carried out to reduce the bacterial load: pre-operative and/or post-operative rinses or gauze impregnated with antimicrobial solutions, such as 0.12%-0.20% chlorhexidine (CHX), 1% peroxide, and 10% povidone-iodine were prescribed in the vast majority of patients, being reported in 9 (90 %) of 10 studies [12,22-26,28,34,35]. Complementary approaches included professional oral hygiene session, in the form of scaling, carried out one week before extraction in one study [24]. In addition, one study added photobiomodulation-laser sessions with Nd:YAG laser, carried out intra-operatively, and post-operatively as weekly session for at least 6 weeks until achievement of mucosal healing [35].

All studies agreed on the necessity to carry out a surgical protocol of teeth extraction as much atraumatic as possible, avoiding excessive manipulation of the soft tissues surrounding the surgical site, with meticulous debridement and curettage of extraction socket, and copious rinse of the alveolar socket, either with saline solution [12] or with povidone-iodine [35]. Smoothening of bone edges was commonly deployed with either piezosurgery alone [24,26], piezosurgery and rongeurs [22,25], or with surgical burs [12,34] (Table 3). Follow-up ranged vastly between the studies, from 12 weeks in an hospital-based case-series [28], up to an average of 41 months in the most recent retrospective study available [12]. Most of the studies reported an average follow-up of one year [22-26,31,34].

Similarly, frequency of MRONJ led to a broad range of 0-13.1%, with no cases were reported in 3 (30%) of 10 studies out of a comprehensive sample of 100 patients [22,23,25], whereas the 13.1% frequency of MRONJ was detected in the only study deploying ampicillin as first-line antibiotic treatment [28].

Dental extraction with no soft tissue closure

Four studies assessed risk of MRONJ among patients treated with IV BPs and exposed to antibiotic prophylaxis for teeth extraction with no soft tissue closure in the last twelve years. Of these, two were retrospective studies [21,32] one prospective study [27], and one case-series [33]. Table 2 and Table 3

show a summary of the perioperative antibiotic regimen, concurrent preventive protocols, and main characteristics of surgical protocol applied in each study.

Data from 176 patients are reported, with size of sample ranging widely from 23 [32] to 95 patients [33]. The most commonly prescribed antibiotic drug was amoxicillin, either alone [33] or combined with clavulanate potassium (CP) [21,27], as reported in 3 (75%) of 4 papers, being administered in a comprehensive sample of 153 patients, with an overall consistent daily dosage of 2-3 grams daily among all studies. Conversely, metronidazole was administered in 23 patients of a retrospective study, as first-line treatment [32]. In each study antibiotics were administered orally, with a duration of 7 days in two papers [21,32], and of 17 days in the two remaining studies, either administered from 2 days before to 15 days after extraction [27] or from 3 days before to 14 days after extraction [33]. Alternative antibiotic treatment was reported in 3 (75%) of 4 studies [21,27,32], mainly due to the possibility of an allergy to β-lactam family, with same route of administration and duration as the first-line treatment. In detail, levofloxacin 500 mg daily [21] and clindamycin 900 mg daily [27], were proposed as second-line treatment in cases of intolerance to amoxicillin, whereas in the retrospective study where metronidazole was the first line of treatment, 1.5 gr of amoxicillin represented the second-line approach [32].

As in the previous subset of studies, these studies deployed techniques other than antibiotics administration to reduce the bacterial load, such as post-operative CHX mouth rinse, reported in 3 of the 4 studies [27,32,33]; one case-series also pursued this aim with a pre-operative professional oral hygiene session, in the form of scaling, carried out one week before extraction in one study, together with intra-operative photobiomodulation-laser sessions with Nd:YAG laser, also carried out post-operatively as weekly sessions for at least 6 weeks, until achievement of mucosal healing [33].

Despite the absence of a flap approach, in these studies the surgical protocol of teeth extraction was commonly combined with copious rinse of the alveolar socket, either with saline solution [32] or with antimicrobial solutions, such as CHX [27], or povidone-iodine [33]. In one paper, meticulous debridement and curettage of extraction socket was also performed [27] (Table 3). Follow-up ranged

vastly between the studies, from 4 months in one study [27], up to an average of 35 (range 20-61) months in the oldest retrospective study available [21]. The remaining two studies reached at least one year of follow-up [32,33].

Similarly, frequency of MRONJ lead to a broad range of 5.26-34.8%, with the widest range of outcome emerging within the same sample of 24 patients retrospectively studied [21], where none (0%) of 10 patients were affected by MRONJ after teeth extraction while under antibiotic coverage, against 8 (57%) of 14 patients who experienced MRONJ after extraction performed under no antibiotic coverage. It is worth reporting that this was the only study capable of providing a differential analysis with a "case-control" concerning the role of antibiotic treatment.

Systemic antibiotic for teeth extraction in patients under PO BPs

Dental extraction with soft tissue closure

Five studies assessed risk of MRONJ among patients treated with PO BPs and exposed to antibiotic prophylaxis undergoing teeth extraction with soft tissue closure in the last ten years. Of these, three prospective studies [29,34,35], one retrospective study [12], and one cohort study [31] were found. Table 2 and Table 3 show a summary of the perioperative antibiotic regimes, concurrent preventive protocols, and main characteristics of surgical protocol deployed in each study.

Data from 771 patients were reported, with size of sample ranging widely from 7 [35] to 700 [29] patients. Just as in IV-BP patients, the most commonly prescribed antibiotic drug remained amoxicillin, either alone [35], or combined with CP [29,34] as reported in 3 (60%) of 5 articles, being administered in a comprehensive sample of 725 patients. Amoxicillin + CP in combination with metronidazole were provided in the smaller counterpart of 16 out of 60 PO-BP patients [31]; similarly, penicillin was administered in 30 PO-BP patients out of an original sample of 84 subjects [12].

As described for IV-BP patients, the most common route of antibiotic prescription was by far the oral route, being reported in 4 (80%) of 5 studies [29,31,34,35], with the only exception represented, once again, by IV penicillin [12]. Duration of antibiotic treatment was mostly within 7 days, as reported in 4 (80%) of 5 studies [12,29,31,34], starting 1-3 days before extraction and ending 2-5 days after extraction. Conversely, antibiotics were administered for more than 2 weeks in only one paper, as the previously described 17-days protocol on 7 of 36 BP patients by the same Author [35]. Alternative antibiotic treatment was reported in 3 (60%) of 5 studies [12,29,31]. Apart from those already described in the previous section [12,31], erythromycin was also administered on PO-BP patients [29]. As detailed for IV-BP patients, concurrent protocols were deployed together with antibiotics to reduce microbial aggression, with antimicrobial solutions, such as 0.12%-0.20% CHX, 1% peroxide, and 10% povidone-iodine used in three studies [12,34,35], pre-operative oral hygiene session in one study [29] and photobiomodulation-laser in one article, with the same specifics reported above for IV-BP counterparts [35]. The same surgical procedure described among IV-BP patients, consisting of an atraumatic, microbiologically secured teeth extraction, with the very same specifics detailed above (Table 3). Follow-up ranged vastly between the studies, from a minimum of 12 months in two studies [31,34], up to 72 months in the largest study available [29]. Differently from what reported amidst IV-BP users, MRONJ affected just 1 out of 771 PO-BP patients enrolled in these studies, with this very single MRONJ case emerging out of the 30 patients of a retrospective study [12], whereas no cases of MRONJ were reported in the remaining 4 articles [29,31,34,35], leading to a raw estimated MRONJ frequency of 0.1% (1/771).

Dental extraction with no soft tissue closure

Three studies assessed risk of MRONJ among patients treated with PO BPs and exposed to antibiotic prophylaxis for teeth extraction in the last seven years. Of these, one prospective study [30], one

retrospective study [32], and one case-series [33] were found. Table 2 and Table 3 show a summary of the perioperative antibiotic regimes, concurrent preventive protocols, and main characteristics of surgical protocol detailed in each study.

Data from 456 patients were reported, with an overall homogeneous size of sample ranging from 122 [33] to 202 [32] patients. Oral amoxicillin alone was prescribed in two studies [30,33] with a short protocol consisting of a 3-days treatment, at a dosage of 250 mg 60 minutes before extraction, followed by 1 gram daily for 2 days after surgery in one paper [30] and a 17-days protocol on 122 of 217 BP patients in another paper [33] Conversely, oral metronidazole was administered in 202 PO-BP patients, which was by far the biggest subset out of an original sample of 225 of individuals [32]. Alternative antibiotic treatment was reported in two papers, either as 1.5 gr amoxicillin daily [32], or as clarithromycin 200 mg 60 minutes before the extraction [30].

To reduce the antimicrobial load, one study detailed use of 10% povidone-iodine solution for intraoperative irrigation, together with pre-operative oral hygiene session and photobiomodulation-laser, with the same specifics reported above for IV-PB counterparts [33]. Follow-up ranged from a minimum of 3 months [30], to an average of 12-15 months [32,33]. Regarding MRONJ occurrence, only 5 of the 202 cases reported in one paper experienced MRONJ [32], with the remaining two papers detailing no MRONJ in their samples [30,33], leading to a raw estimated MRONJ frequency of 1% (5/456).

Systemic antibiotic for teeth extraction in patients under denosumab

Only one retrospective study examined an appropriate tooth extraction method comprehensive of a peri-operative prophylaxis with systemic antibiotics, with the aim to assess frequency of MRONJ among patients undergoing treatment with denosumab [36]. Table 1-3 summarize its main characteristics. Briefly, 19 patients were exposed to a 2-days antibiotic regimen consisting of a first administration of 10,000,000 IU of IV penicillin before surgery, and a second one after teeth extraction. IV 600 mg

clindamycin thrice daily was designed as second-line treatment in case of allergy. Concurrent risk-reducing protocols consisted in providing instructions for a soft diet, and limitation in wearing dentures during healing time. With a surgical protocol of atraumatic extraction, smoothening of bone edges and wound closure with tension-free mucoperiostal flap (Table 3), only 1 out of 19 cases of MRONJ was detected, with a raw MRONJ frequency of 2.5%.

Risk of bias of the included studies

QUIPS Tool revealed an overall moderate/high risk of bias within each study. Table 4 provides the detailed analysis for each study. In detail, the "study participation" domain was overall properly reported, leading to a low-moderate risk of bias, as it was similarly described among the various studies [12,21-36], with information provided on the baseline characteristics, such as age/sex distribution, type of BP/biologic agent administered, underlying disease [12, 21-28,30,32-36]. A worthy exception must be pointed out in two studies, in which no precise distribution of patients was given with regards to either the type of cancer [29] or the bone metabolic disorder [31]. Timing of enrolment was mostly provided [12,21-27,29-34,36], whereas a thorough list of eligibility criteria was reported only in some papers [12,22,24-26,29-31].

The "attrition bias" domain was mostly deemed uncertain, with no clear information provided on the dropout rates of patients in most of the included studies [12,24,25,27,28,30,31,33-36].

Concerning the "prognostic factor measurement", as the antibiotic treatment, the main characteristics in terms of type of drug, duration of treatment and dosage were commonly reported, as previously mentioned, [12,21,22,24-36], with the sole exception of one study, where no detailed information was given concerning the antibiotic administered as second-line treatment [23]. However, it is worth noticing that no data regarding the exact ratio of first-line vs second-line antibiotic administration was provided in any of the included studies.

Likewise, the “outcome measurement”, as MRONJ definition, was overall properly detailed, with the sole exception of the most recent study [12], as detailed in the previous paragraphs.

Finally, a predominant moderate-high risk was detected concerning the two most important domains, “study confounding” and “statistical analysis and reporting”, which are vital to assess the strength of association between the prognostic factor (i.e., antibiotics) - and the outcome (i.e., MRONJ).

With many preoperative, intraoperative and postoperative approaches conducted together with antibiotics in the vast majority of the included studies, as detailed in the previous paragraphs and reported in Table 2-Table 3, a proper statistical evaluation was not pursued in any of the included studies [12,22-29,36], with the sole exception of one paper focusing its effort precisely on the role of antibiotic prophylaxis as a protecting factor against MRONJ, through a “case-control” approach [21].

Discussion

The present review described the main characteristics of the most detailed antibiotic protocols provided in literature among patients in need of dental extractions at risk of developing MRONJ. Due to heterogeneity in study design, size of samples, combinations of differential concurrent protocols, duration and dose of antibiotic treatments, and with no RCT available, a meta-analysis could not be provided. Concerning the type of antibiotic, it can be concluded that the protocols empirically described in literature revolved around a penicillin-based antibiotic, either alone or accompanied by a β-lactamase inhibitor or metronidazole. In this sense, oral amoxicillin can be regarded as the most commonly deployed drug, being provided as first-line treatment in 76.4% of the 17 studies included in the present review [21-27,29,31,33-35]. With regard to the length of antibiotic treatment before and after tooth extraction, no uniform approach can be deduced among patients receiving treatment with PO and/or IV-BP, ranging from 3 days [30] to 20 days [23], with an average of 6.5 as the most recurrent timespan ensured, despite being provided in slightly less than half (47%) of the studies [22,24-26,28,29,31,34]. Furthermore, it cannot be determined which long-term or short-term duration of postoperative antibiotics has the most positive effect on surgical outcomes in MRONJ patients. Such limitations are intertwined with the empirical nature of these protocols, applied against a clinical entity, such as MRONJ, whose etiopathogenesis has not been completely elucidated [38], especially when it comes to the role of infection, whose role is still debated as either major, or secondary to the increased malfunction of osteoclast and the reduced bone turnover [39]. Despite the predominance of Actinomyces species within MRONJ lesions from various reports over the last decade, with frequency ranging from 39 to 100%, usually followed by Streptococcus, Prevotella and Klebsiella species, the most recent evidence suggested that the interaction between the different members of the microflora, of which very little is known, might be more important than the actual predominance of individual phylotypes [39,40]. It has been speculated that a complex biofilm capable of an ever-changing combination of Gram+/Gram-, and aerobe-anaerobe

ratio might carve its way through from the first phases of mucosal infection, down to the in-depth bone colonization, culminating with onset of MRONJ [39,40].

In support of this hypothesis, a recent report on 71 samples of MRONJ patients showed significant differences in the composition of microbial organisms responsible of soft tissue infection when compared to their own bony counterpart, with Actinomyces species being found in significantly higher concentration in the former (19.2%) than in latter (9.9%), and Streptococcus, Prevotella and Veillonella spp. detectable in abundance in both districts [41]. With regards to these aspects, it is worth pointing out that in none of the studies the empiric antibiotic regimen was tailored based on differential microbiologic findings between patients, nor was it changed accordingly, in those cases in which MRONJ occurred after teeth extraction, despite the ongoing prophylaxis. Main strength of this review relies in the detailed and extensive focus on the antibiotic protocols so far deployed to reduce risk of MRONJ on patients in need of teeth extraction while undergoing treatment with BP or antiresorptive agents, differently from previous reviews, where this aspect was conveyed far more broadly [18-20]. However, some limitations must be highlighted. Apart from the empirical nature of evidence described, this study aimed to survey the important studies limiting its scope of research to PubMed/MEDLINE and SCOPUS databases. Thus, it is possible that some potentially pertinent studies may not have been identified. However, a concurrent research of inherent studies from the references of previous similar reviews of literature was introduced in our methodology, to compensate for this limit. Secondly, a great variability of surgical protocols pursued within the included studies emerged. To compensate this aspect and provide a more homogeneous design to the present review, the various extraction protocols were grouped in two major categories - soft tissue closure vs no soft tissue closure - both for PO BF and IV BF patients. Interestingly, such approach led to the quantification of a raw discrepancy in frequency of MRONJ between a flap-reliant dental extraction technique and flapless approach, both across IV BP patients (0-13% vs 5-57%, respectively) and amid PO BP patients (0.1% vs 1%, respectively), suggesting a potential higher safety of the former technique against the latter.

A third limitation lies in the great variability of methods and the absence of experimental trials prevented from acquisition of meta-analytic data, despite the absence of controlled clinical trials or randomized-controlled trials on the administration of antibiotics among patients under treatment with BP, which would have required an arm of patients under no antibiotic coverage whatsoever, is completely understandable due to ethical reasons, particularly with regards to cancer patients. In line with what acquired from the 17 clinical studies included, and the microbiologic evidence of high susceptibility to beta-lactam antibiotics by Actinomyces and other species most commonly associated to MRONJ [42], especially when combined with beta-lactamase inhibitors, such combination should still be regarded as first line of treatment for patients undergoing extraction when exposed to BMAs agents. However, use of antibiogram should be recommended more often, especially in cases of extensive involvement of infection on the soft tissues, where antibiotics ought to be unable to provide symptom relief and/or downsize of the infective clinical pattern associated with the unhealed alveolar socket [9]. Such attention for microbiologic aspects is of primary importance when it comes to dental extraction, since it is one of the most significant risk factors for the development of MRONJ, and by far the most common association experienced by oral surgeons and general dental practitioner. In fact, as reported in a recent international consensus [9], extraction has been classified as the fourth most common risk factor among oncology population, after IV BP, denosumab, and radiation therapy, landing at third place after suppuration, and type of BP, amid osteoporotic patients.

As detailed in the Results section, risk of MRONJ after teeth extraction seems to be, on average, at least ten times higher among IV BP patients (0-34.8%), rather than in PO BP population (0% - 3.3%), when under antibiotic coverage, with an isolated and worrisome percentage of 57% in the only study available where no antibiotic coverage was provided [21]. However, difference in potency and duration of BP treatment, surgical procedures, and technique of wound closure are known to play a parallel role in defining the overall risk of MRONJ. As suggested in a recent systematic review [43], alveolectomy and placement of biological membrane enriched with growth factors can significantly diminish MRONJ risk

in IV BP patients, from 4.45 to 0.91%, and from 4.4% to 0.91%, respectively, being instead not significant in PO BP patients. On the contrary, primary wound closure did not seem to be as significant, providing a slight reduction of MRONJ risk amid IV BP patients. In summary, despite antibiotic coverage has been empirically considered as undeniable in reducing risk of MRONJ on patients subjected to tooth extraction while treated with antiresorptive or antiangiogenic drug, no conclusive scientific evidence is available to ponder the role of antibiotics in decreasing this possibility, due to the absence of papers providing experience of patients unexposed to antibiotics before/after teeth extractions. As a consequence, no scientific evidence is available to determine which antibiotic protocol, among those described so far in literature, and detailed for the first time in the present review, can be more reliable in providing the most consistent risk reduction of MRONJ onset, whenever tooth extraction is needed. Further clinical studies combining clinical outcomes to microbiologic findings of patients experiencing MRONJ in sites of extraction are warranted, as a first step towards a standardized, evidence-based driven, protocol of perioperative antibiotic prophylaxis for BP and BMA-patients in need of dental extraction.

In conclusion, empirical data acquired from case-series, prospective and retrospective studies suffering of moderate/high risk of bias suggest that 2-3 gr of amoxicillin daily, either alone or in combination with CP, for 6-7 days is the most-commonly deployed antibiotic treatment to minimize risk of MRONJ in patients under oral and intravenous bisphosphonates in need of dental extraction, with soft tissue closure techniques potentially providing further reduction of MRONJ risk. With only a small case-series of 19 patients under denosumab found, there is insufficient data to understand if the aforesaid antibiotic protocol can be applied to patients exposed to the new generation of antiresorptive, bone-modifying agents. Combination of clinical and microbiologic data is needed to establish the main characteristics of a reliable perioperative antibiotic regimen for patients necessitating dentoalveolar surgical procedures like tooth extractions.

Acknowledgments

None.

Conflict of interest

None.

References

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B et al**.** (2014) American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 72, 1938-1956.
2. Marx RE (2003) Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 61, 1115-1117.
3. Estilo CL, Fornier M, Farooki A, Carlson D, Bohle G 3rd, Huryn JM (2008) Osteonecrosis of the jaw related to bevacizumab. J Clin Oncol 26, 4037-4038.
4. Taylor KH, Middlefell LS, Mizen KD (2010) Osteonecrosis of the jaws induced by anti-RANK ligand therapy. Br J Oral Maxillofac Surg 48, 221-223.
5. Fleissig Y, Regev E, Lehman H (2012) Sunitinib related osteonecrosis of jaw: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol 113, e1-3.
6. Eguia A, Bagán-Debón L, Cardona F (2020) Review and update on drugs related to the development of osteonecrosis of the jaw. Med Oral Patol Oral Cir Bucal 25, e71-e83.
7. Krüger TB, Sharikabad MN, Herlofson BB (2013) Bisphosphonate-related osteonecrosis of the jaw in four Nordic countries and an indication of under-reporting. Acta Odontol Scand 71, 1386-1390.
8. Kim HY, Kim JW, Kim SJ, Lee SH, Lee HS (2017) Uncertainty of current algorithm for bisphosphonate-related osteonecrosis of the jaw in population-based studies: a systematic review. J Bone Miner Res 32, 584-591.
9. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F et al**.** (2015) Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 30, 3-23.

10. Polidoro S, Broccoletti R, Campanella G, Di Gaetano C, Menegatti E, Scoletta M et al**.** (2013) Effects of bisphosphonate treatment on DNA methylation in osteonecrosis of the jaw. Mutat Res 757, 104-113.
11. McGowan K, McGowan T, Ivanovski S (2018) Risk factors for medication-related osteonecrosis of the jaws: a systematic review. Oral Dis 24, 527-536.
12. Spanou A, Nelson K, Ermer MA, Steybe D, Poxleitner P, Voss PJ (2020) Primary wound closure and perioperative antibiotic therapy for prevention of bisphosphonate-related osteonecrosis of the jaw after tooth extraction. Quintessence Int 51, 220-228.
13. Katsarelis H, Shah NP, Dhariwal DK, Pazianas M (2015) Infection and medication-related osteonecrosis of the jaw. J Dent Res 94, 534-539.
14. Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C (2013) Assessing bias in studies of prognostic factors. Ann Intern Med 158, 280-286.
15. Utreja A, Almas K, Javed F (2013) Dental extraction as a risk factor for bisphosphonate related osteonecrosis of the jaw in cancer patients: an update. Odontostomatol Trop 36, 38-46.
16. Kyrgidis A, Tzellos TG, Toulis K, Arora A, Kouvelas D, Triaridis S (2013) An evidence-based review of risk-reductive strategies for osteonecrosis of the jaws among cancer patients. Curr Clin Pharmacol 8, 124-134.
17. Poxleitner P, Engelhardt M, Schmelzeisen R, Voss P (2017) The prevention of medication-related osteonecrosis of the jaw. Dtsch Arztebl Int 114, 63-69.
18. Bermúdez-Bejarano EB, Serrera-Figallo MÁ, Gutiérrez-Corrales A, Romero-Ruiz MM, Castillo-de-Oyagüe R, Gutiérrez-Pérez JL et al**.** (2017) Prophylaxis and antibiotic therapy in management protocols of patients treated with oral and intravenous bisphosphonates. J Clin Exp Dent 9, e141-149.

19. Diniz-Freitas M, Limeres J (2016) Prevention of medication-related osteonecrosis of the jaws secondary to tooth extractions. A systematic review. Med Oral Patol Oral Cir Bucal 21, e250-259.
20. Karna H, Gonzalez J, Radia HS, Sedghizadeh PP, Enciso R (2018) Risk-reductive dental strategies for medication related osteonecrosis of the jaw among cancer patients: a systematic review with meta-analyses. Oral Oncol 85, 15-23.
21. Montefusco V, Gay F, Spina F, Miceli R, Maniezzo M, Teresa Ambrosini M et al**.** (2008) Antibiotic prophylaxis before dental procedures may reduce the incidence of osteonecrosis of the jaw in patients with multiple myeloma treated with bisphosphonates. Leuk Lymphoma 49, 2156-2162.
22. Ferlito S, Liardo C, Puzzo S (2010) Dental extractions in patient treated with intravenous bisphosphonates and risk of osteonecrosis of jaws: presentation of a preventive protocol and case series. Minerva Stomatol 59, 593-601.
23. Lodi G, Sardella A, Salis A, Demarosi F, Tarozzi M, Carrassi A (2010) Tooth extraction in patients taking intravenous bisphosphonates: a preventive protocol and case series. J Oral Maxillofac Surg 68, 107-110.
24. Scoletta M, Arduino PG, Pol R, Arata V, Silvestri S, Chiecchio A et al**.** (2011) Initial experience on the outcome of teeth extractions in intravenous bisphosphonate-treated patients: a cautionary report. J Oral Maxillofac Surg 69, 456-462.
25. Ferlito S, Puzzo S, Liardo C (2011) Preventive protocol for tooth extractions in patients treated with zoledronate: a case series. J Oral Maxillofac Surg 69, e1-4.
26. Scoletta M, Arata V, Arduino PG, Lerda E, Chiecchio A, Gallesio G et al**.** (2013) Tooth extractions in intravenous bisphosphonate-treated patients: a refined protocol. J Oral Maxillofac Surg 71, 994-999.

27. Sanchis JM, Bagán JV, Murillo J, Díaz JM, Asensio L (2014) Risk of developing BRONJ among patients exposed to intravenous bisphosphonates following tooth extraction. Quintessence Int. 45, 769-777.
28. Bodem JP, Kargus S, Eckstein S, Saure D, Engel M, Hoffmann J et al. (2015) Incidence of bisphosphonate-related osteonecrosis of the jaw in high-risk patients undergoing surgical tooth extraction. J Craniomaxillofac Surg 43, 510-514.
29. Mozzati M, Arata V, Gallesio G (2013) Tooth extraction in osteoporotic patients taking oral bisphosphonates. Osteoporos Int 24, 1707-1712.
30. Shudo A, Kishimoto H, Takaoka K, Noguchi K (2018) Long-term oral bisphosphonates delay healing after tooth extraction: a single institutional prospective study. Osteoporos Int 29, 2315-2321.
31. Saia G, Blandamura S, Bettini G, Tronchet A, Totola A, Bedogni G et al. (2010) Occurrence of bisphosphonate-related osteonecrosis of the jaw after surgical tooth extraction. J Oral Maxillofac Surg 68, 797-804.
32. Taylor T, Bryant C, Popat S (2013) A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King's College Hospital. Br Dent J 214, E18.
33. Vescovi P, Meleti M, Merigo E, Manfredi M, Fornaini C, Guidotti R et al. (2013) Case series of 589 tooth extractions in patients under bisphosphonates therapy. Proposal of a clinical protocol supported by Nd:YAG low-level laser therapy. Med Oral Patol Oral Cir Bucal 18, e680-685.
34. Heufelder MJ, Hendricks J, Remmerbach T, Frerich B, Hemprich A, Wilde F (2014) Principles of oral surgery for prevention of bisphosphonate-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol 117, e429-435.
35. Vescovi P, Giovannacci I, Merigo E, Meleti M, Manfredi M, Fornaini C et al. (2015) Tooth extractions in high-risk patients under bisphosphonate therapy and previously affected with

osteonecrosis of the jaws: surgical protocol supported by low-level laser therapy. J Craniofac Surg 26, 696-699.

36. Matsumoto A, Sasaki M, Schmelzeisen R, Oyama Y, Mori Y, Voss PJ (2017) Primary wound closure after tooth extraction for prevention of medication-related osteonecrosis of the jaw in patients under denosumab. Clin Oral Investig 21, 127-134.
37. Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B; American association of oral and maxillofacial surgeons (2009) American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaws—2009 update. J Oral Maxillofac Surg. 67, 2-12.
38. Lombard T, Neirinckx V, Rogister B, Gilon Y, Wislet S (2016) Medication-related osteonecrosis of the jaw: new insights into molecular mechanisms and cellular therapeutic approaches. Stem Cells Int 2016, 8768162.
39. Kumar SK, Gorur A, Schaudinn C, Shuler CF, Costerton JW, Sedghizadeh PP (2010) The role of microbial biofilms in osteonecrosis of the jaw associated with bisphosphonate therapy. Curr Osteoporos Rep 8, 40-48.
40. Hinson AM, Smith CW, Siegel ER, Stack BC Jr (2014) Is bisphosphonate-related osteonecrosis of the jaw an infection? A histological and microbiological ten-year summary. Int J Dent 2014, 452737.
41. Zirk M, Wenzel C, Buller J, Zöller JE, Zinser M, Peters F (2019) Microbial diversity in infections of patients with medication-related osteonecrosis of the jaw. Clin Oral Investig 23, 2143-2151.
42. Brook I (2008) Actinomycosis: diagnosis and management. South Med J. 101, 1019-1023.
43. Abt E (2017) The risk of medication-related osteonecrosis of the jaw after dental extraction is higher for patients on intravenous as compared with oral antiresorptive drugs. J Evid Based Dent Pract 17, 105-106.