Bone 141 (2020) 115676

Contents lists available at ScienceDirect

Bone

journal homepage: www.elsevier.com/locate/bone

Review Article

Adjuvant therapies for MRONJ: A systematic review

Dries Govaerts[a,b], Frederik Piccart[a,b], Anna Ockerman[a], Ruxandra Coropciuc[a,b], Constantinus Politis[a,b], Reinhilde Jacobs[a,c,*]

[a] OMFS–IMPATH Research Group, Department of Imaging and Pathology, Faculty of Medicine, Catholic University Leuven, Belgium
[b] Department of Oral and Maxillofacial Surgery, University Hospitals Leuven, Leuven, Belgium
[c] Department of Dental Medicine, Karolinska Institute, Stockholm, Sweden

ARTICLE INFO

Keywords:
Osteonecrosis
Medication-related osteonecrosis of the jaw
Therapy
laser ablation
LPRF
Bisphosphonates
Denosumab

ABSTRACT

Objective: Medication-related osteonecrosis of the jaw (MRONJ) is a severe adverse reaction caused by the use of antiresorptive antiangiogenic medication. Treating MRONJ is difficult and besides standard treatments, which are conservative medical and surgical approaches, there are some adjuvant therapies that might further stimulate healing. The aim of this systematic review is to compare outcome and effectiveness of currently available adjuvant therapies for MRONJ.

Methods: This systematic review was conducted following the PRISMA guidelines. Articles focusing on mucosal healing in patients treated with an adjuvant therapy for MRONJ were selected and analysed. Inclusion was not limited to randomized controlled trials to present a complete review of the current literature.

Results: A search was performed in Pubmed, Embase, Web of Science and Cochrane Central Register of Controlled Trials. Thirty articles out of 3297 were included. Laser ablation had a success of 60–95% for complete healing. The controlled trials of leukocyte- and platelet-rich-fibrine (LPRF) showed 60–100% success for the same outcome. Fluorescence guided surgery had a complete healing percentage of 85–90%.

Conclusions: The results suggest that laser ablation, LPRF and fluorescence guided surgery might have a potential in improving the healing process. Interpreting the results should however be done with great care and a critical point of view, as most articles had a medium to high risk of bias. More randomized controlled trials are necessary to define the most beneficial therapy protocols.

Clinical relevance: It seems that adjuvant surgical therapies for treating MRONJ are beneficial for mucosal healing, but there is only low scientific evidence.

1. Introduction

Bisphosphonates (BP) inhibit osteoclastic activity, thereby suppressing bone turnover. Next to antiresorption, BP also have an antiangiogenic and anticancer activity [1]. Antiresorptive medications play an important role in the treatment of various bone resorptive diseases. Medication-related osteonecrosis of the jaw (MRONJ) was reported for the first time in 2003 by Marx [2] and clearly acknowledged in the following years [3–5].

Next to BP, denosumab [6,7] (RANKL inhibitor), bevacizumab [8,9] (monoclonal antibody; inhibitor of VEGF-A, avascular growing factor), sunitinib [9,10] (tyrosine kinase inhibitor) and temsirolimus [8] (specific mTOR inhibitor) are other risk factors for MRONJ. As more and more anti-resorptive and antiangiogenic drugs are being developed, there is a risk that these new drugs will increase the incidence of MRONJ. The risk of developing MRONJ in cancer patients goes up to 6.7% or 1.9% when zoledronate or denosumab are administered respectively [11]. Based on the current literature, for osteoporotic patients, the MRONJ risk goes up to 0.21% when exposed to oral BP for longer than four years and up to 0.04% receiving intravenous (IV) BP or denosumab [11].

The current definition of MRONJ is based on three characteristics: 1) current or previous treatment with antiresorptive or antiangiogenic agents, 2) exposed jaw bone or bone that can be probed through an intraoral or extra-oral fistula in the maxillofacial region that has persisted for longer than 8 weeks, 3) no history of radiation therapy to the jaws or obvious metastatic disease to the jaws [11]. It is important to keep in mind that patients at risk can present with other clinical conditions not to be confused with MRONJ. Common misdiagnosed conditions include, but are not limited to, osteitis, fibro-osseous lesions and chronic sclerosing ostemyelitis [11].

MRONJ is divided in five stages, which are the following: At risk

* Corresponding author at: Omfsimpath Research Group, Department of Imaging and Pathology, KU Leuven, Kapucijnenvoer 33, Leuven 3000, Belgium.
E-mail address: reinhilde.jacobs@uzleuven.be (R. Jacobs).

https://doi.org/10.1016/j.bone.2020.115676
Received 29 June 2020; Received in revised form 29 September 2020; Accepted 1 October 2020
Available online 03 October 2020

stage, no apparent necrotic bone in patients treated with antiresorptive treatment. Stage 0 is defined as no clinical evidence of necrotic bone but present with nonspecific symptoms or clinical and radiographic findings. Stage 1 is defined as exposed and necrotic bone or a fistula that probes to bone in patients who are asymptomatic and have no evidence of infection. Stage 2 is defined as exposed and necrotic bone or a fistula that probes to bone with evidence of infection. These patients are symptomatic Stage 3 is defined as exposed and necrotic bone or fistulas that probe to bone with evidence of infection and at least 1 of the following: exposed necrotic bone extending beyond the region of alveolar bone (ie, inferior border and ramus in the mandible, maxillary sinus, and zygoma in the maxilla), pathologic fracture, extraoral fistula, oral antral or oral nasal communication or osteolysis extending to the inferior border of the mandible or sinus floor [11].

The most controversial topic about MRONJ is its management. The current main treatment styles for MRONJ are medical conservative (long term antibiotics and antiseptics) and surgical (ranging from debridement to segmental resection to free flap reconstruction). The guidelines state that therapy should be stage specific, suggesting a medical conservative approach for stage 0 and I, a minimally invasive surgical approach for stage II and a radical surgical approach for stage III [11].

According to some studies, both medical conservative and surgical approaches might be optimized by adding an unconventional but adjuvant therapy to improve the healing process [12–15]. Several recent studies proposed their alternative protocol to prove their effectiveness. As treating MRONJ can be challenging, preventive approaches, surgery and adjuvant therapy should be considered.

A wide variety of adjuvant therapies exist, which we describe in short hereafter. For example, Hyperbaric Oxygenation Therapy (HBO) augments the availability of reactive oxygen in the body and signalling for bone turnover may be increased [16]. Also, necrotic bone can be vaporized by Laser Ablation and is linked to a faster bone healing without risk for thermal increase [17]. While Low Level Laser Therapy (LLLT) stimulates cell proliferation and bone formation through induction of cell-cycle regulatory proteins [17,18]. Leukocyte- and Platelet Rich Fibrin (LPRF) and its variations (Platelet Rich Fibrin (PRF), Platelet Rich Plasma (PRP) or Leukocyte- and Platelet Rich Plasma (LPRP)) are used for the amelioration of bone healing and showed a significant improvement of terms of quality of life [19]. To stimulate the antioxidant system and increasing of red blood cells and haemoglobin concentration, Ozone Therapy can be used [20]. An adjuvant surgical technique is called Fluorescence Guided Surgery which highlights the transition from necrotic to vital bone during debridement [21]. Teriparatide (TPTD) can reactivate bone formation by stimulation osteoblasts and osteoclasts [22] and Bovine Lactoferrin (bLf) contains an anti-inflammatory effect [23], whereas recombinant human bone morphogenetic protein-2 (rhBMP-2) has osteoconductive effects and increases bone remodeling [24]. The toxicity of bisphosphonates may be reversed by Geranylgeraniol (GGOH) [25]. While Mesenchymal stem cells (MSC) owns the potential to differentiate into different cell lineages [26]. Last, Pentoxifylline and tocopherol (PENTO) are widely used for treatment of osteoradionecrosis, by inhibiting inflammation and protecting cell membranes, thus possible improving healing of MRONJ lesions [27].

Despite the variety of available reports on different adjuvant therapies, their differential indications and potential therapeutic effects have not yet been contrasted and compared. Therefore, the aim of this systematic review is to determine the differences in outcome and to evaluate the effectiveness of various adjuvant therapies for MRONJ.

2. Methods

2.1. Protocol and registration

This systematic review was performed following the PRISMA (Preferred Reporting items for Systematic Reviews and Meta-Analysis) guidelines to ensure the quality, transparency and comprehensiveness of the review. A search strategy was specified in advance and registered at PROSPERO (International prospective register of systematic reviews; registration number: CRD42019124062).

2.2. Eligibility criteria

The following criteria were employed for inclusion of papers in this review:

Type of studies: Since we were searching for unconventional therapies for MRONJ, which is a recent pathology due to the use of bisphosphonates or denosumab, we were all-inclusive and considered case-controls, cohort studies, non-randomized trials and randomized controlled trials. There was no exclusion based on the follow-up period, but we are aware that the follow-up period was important for a potential risk of bias. Accordingly, we assessed the follow-up in the risk of bias and provided information in the risk of bias table.
Type of participants: Studies evolving patients diagnosed with MRONJ and treated with a non-standardized, adjuvant treatments were included.
Type of intervention and comparisons: All possible unconventional treatments to manage MRONJ, such as bone morphogenetic protein-2, geranylgeraniol, hyperbaric oxygen therapy, bovine lactoferrin, laser ablation, low-level laser therapy, mesenchymal stem cells, leukocyte-platelet rich fibrin or platelet-rich plasma, ozone therapy, pentoxifylline and tocopherol, unconventional surgical techniques, teriparatide and more.
Type of outcome measures: Studies evaluating the improvement or completion of mucosal healing and the length of follow up.

The overall overview of the inclusion criteria:

- The use of an adjuvant therapy for the treatment of MRONJ
- Detailed information of the adjuvant therapy
- Outcome measures described by mucosal healing

An adjuvant therapy is a treatment that is complementary to the standard medical conservative or surgical care and improves healing of MRONJ.

Studies were excluded on basis of the following criteria: articles describing only standard conservative (antibiotics and antiseptics) and standard surgical (debridement or sequestrectomy) therapy, systematic reviews, case-reports, case series, ex vivo/in vitro studies, animal studies and articles on osteoradionecrosis.

2.3. Information sources

The search strategy was developed for Pubmed and appropriately modified for Embase, Web of Science and Cochrane Central Register of Controlled Trials, which we accessed through the University of Leuven. The databases were screened on the 1st of April 2020 for eligible articles. In addition, the reference lists of all included full-text articles were screened manually for potential useful articles.

2.4. Search

The search strategy was based on a combination of Medical Subject Headings (MeSH) and free text terms. No filter, nor a time limit or other data restrictions were used when searching the electronic bibliographic databases. The search strategy used for Pubmed can be found in Appendix A.

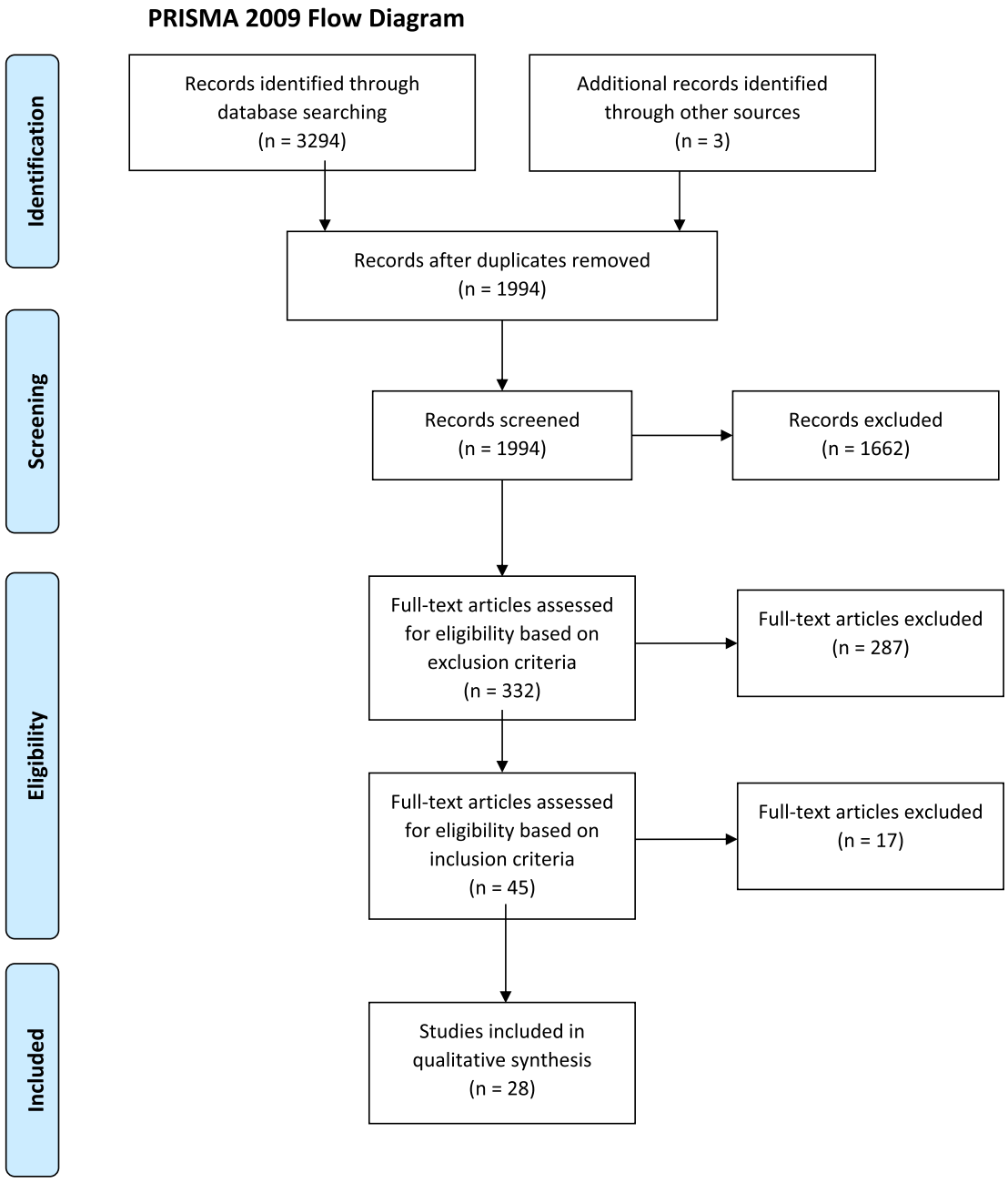

Fig. 1. PRISMA flow chart outlining the study selection process.

2.5. Study selection

Two reviewers (D.G. and F.P.) independently screened the titles and abstracts and obtained a consensus about the inclusion of articles. If they disagreed about inclusion or exclusion, a third (senior) reviewer (R.J.) was consulted, who decided about the matter. In case of articles concerning extension of an original sample, only one article with the most recent data and the most relevant information (*P*-values) was considered for inclusion.

2.6. Data collection process

The data extraction and collection process was performed by a single author (D.G.) according to the Cochrane data extraction form [28] and supervised by the other authors (R.C. and R.J.). If data was missing or when a possibility of misinterpreting the data existed, the concerning authors of potentially eligible articles were contacted for clarification.

2.7. Data items

The following data were collected:

Methods: study design, level of evidence by Cochrane Library [29] adapted from Oxman [30], year of publication, recruitment period.
Participants: Number of participants and demographics (mean age, women/men ratio, ratio of initial diagnoses, ratio of ONJ staging as applicable and bisphosphonates ratio).
Intervention: Details regarding the adjuvant treatment, subgroups per article, use of antiseptics, antibiotics and conservative surgery.
Outcome: Outcome measures (mucosal healing) and follow-up (interval).

Mucosal healing was divided in three categories (complete healing, improvement of healing, no improvement of healing) following the categories of healing in the majority of the included articles. Complete healing was considered when mucosal coverage of the lesion was achieved. Improvement of healing is defined as partial healing or as the transition from a higher to a lower stage of MRONJ. No improvement covers a stabile lesion, meaning no change in MRONJ-staging, or a progression of the lesion.

In the majority of included articles, results of mucosal healing were stated in text form or in tables as defined in this systematic review. When the results of a category were absent, they were calculated as possible or the author was contacted. The three categories were converted to a percentage ratio to allow a more homogenous and comparative overview, with results of mucosal healing presented in a summary table.

2.8. Risk of bias in individual studies

Given the heterogeneity of the study designs, the Newcastle-Ottawa Scale (NOS) was used for evaluation of the risk of bias of the included studies [31,32]. Two authors (D.G. and F.P.) independently performed risk of bias assessment. Any disagreement was resolved by discussion and seeking consensus or consultation of a third author (R.J.) for a conclusive decision. The risk of bias of all studies was judged via a star ranking system. The NOS is divided in a selection domain, a comparability domain and an outcome domain. The three domains together reflect the overall risk of bias, and are based on assigning a rank of zero to nine stars. Studies were categorized as 'Low risk' (6–9 stars), 'Medium risk' (3–5 stars) and 'High risk' (0–2).

3. Results

3.1. Study selection

The flow diagram resuming the selection process is presented in Fig. 1. Through searching the databases mentioned above, 3294 records were identified. In addition, 3 records were added trough manual searching. After removing the duplicates, titles and abstracts of 1994 unique articles were screened, and 332 articles were included for full-text analysis. Finally, 45 articles were assessed for eligibility based on the inclusion criteria. Seventeen articles [33–49] did not met inclusion criteria (Table 1), resulting in 28 studies [16,17,19–21,23,24,50–70] included for a qualitative synthesis. It must be noted that Vescovi et al. [34,42,43,46,47,50] reported broadly on adjuvant treatments using a sample that extended over time. Solely the most recent article was included [50] while the other were excluded to prevent double reporting.

3.2. Study characteristics

Four of the 28 included studies were Randomized Controlled Trials (RCT) [16,19,24,69]. Three studies had a prospective controlled design [23,53,63] while seven studies had a retrospective controlled design [21,50,51,54,64,67,70]; seven studies [17,55,57,58,61,62,65] had a prospective uncontrolled design and seven studies [20,52,56,59,60,66,68] had a retrospective uncontrolled design.

Based on the level of evidence tool adapted from Oxman [30], one study had level I [24]; four studies had level II [16,19,21,69]; nine studies had level III [23,50,51,53,54,63,64,67,70]; no study had level IV (non-randomized historical cohort studies) and fourteen studies had level V [17,20,52,55–62,65,66,68]. Level I represents the highest level of evidence.

Adjuvant treatments proposed in the papers were either HBO [16,68], a combination of laser ablation and LLLT [17,50,69,70], only LLLT [51,52,65], LPRF and its variations [19,24,53–58,66,67], Ozone [20,59,60], Fluorescence guided surgery [21,61,62], Teriparatide [63,64] and Bovine Lactoferrin [23]. One study combined laser ablation and LPRF [58], one study combined laser ablation, LLLT and LPRF [17] and one study combined BMP-2 and LPRF [24] as adjuvant therapy.

Between 7 and 151 patients were selected for each study with a median of 25 patients. The mean age of subjects in the study samples ranged from 55 to 76 years old. Two studies did not report the mean age [23,68]. Gender distribution ranged from 38%–93% (male) and 7–62% (female). Two studies only reported on outcome in women [63,66].

Most of the studies included patients with oncologic as non-oncologic primary diagnoses. Seven studies reported only oncologic primary diagnoses [23,54,56,58,61,62,69]; two studies only multiple myeloma [53,59]. Two studies, both focusing on teriparatide, had only osteoporosis as primary diagnosis [63,64].

Stage I, II and III MRONJ were presented in 12 studies [16,17,21,24,50–52,54,62,65,66,70], three papers focused on stage II MRONJ [23,55,56], two studies had only patients with stage I or II MRONJ [58,69] and another five studies had stage II or III MRONJ patients [19,57,61,64,67]. Six studies [20,53,59,60,63,68] didn't mention the staging of their study sample. Three out of these six studies [20,59,68] were published in 2007, before any position paper was written [5].

In all but five articles, patients were treated with only bisphosphonates for their primary diagnosis. Three studies selected patients

Table 1
Articles discarded not meeting the inclusion criteria.

Author, year	Reason for exclusion
Agrillo et al., 2006 [33]	Providing a protocol in treatment of MRONJ, no report of results
Vescovi et al., 2007 [34]	Same study sample as Vescovi et al. [50]
Vescovi et al., 2008 [42]	Same study sample as Vescovi et al. [50]
Vescovi et al., 2010 [43]	Same study sample as Vescovi et al. [50]
Sweeny et al., 2012 [44]	No MRONJ patient population
Andriani et al., 2012 [45]	No detailed information on the complementary therapy, combining 2 subgoups with different coplementary therapies (HBO and Ozone) as one subgroup
Vescovi et al., 2012 [46]	Same study sample as Vescovi et al. [50]
Vescovi et al., 2012 [47]	Same study sample as Vescovi et al. [50]
Franco et al., 2014 [48]	Reporting on overall healing, no therapy-specific subgroup results
Vescovi et al., 2015 [49]	Reporting on healing of tooth sockets after extraction in a MRONJ population
Fleisher et al., 2016 [35]	No specifications or results on patient subgroup treated with complementary therapy
Mücke et al., 2016 [36]	Reporting on overall healing, no therapy-specific subgroup results, no adjuvant treatment
Jung et al., 2017 [37]	No outcome of mucosal healing
Asaka et al., 2017 [38]	Reporting on healing of tooth sockets after extraction in a MRONJ population
Hadaya et al., 2018 [39]	variation on post-operative wound care, no complementary therapy
Valente et al., 2019 [40]	Multiple treatments until complete healing, no outcome of mucosal healing
Tartaroti et al., 2020 [41]	No outcome of mucosal healing

Table 2
Overview of included studies with outcome presented as complete, improvement or no improvement for healing. The level of evidence, intervention and control groups, use of antiseptics, antibiotics or conservative surgery, healing outcomes and significance are shown.

Author, year	LOE	Patient groups (n (sites))	AS?	AB?	CS?	HEALING (in general)			Significance	What is significant?
						Complete healing	Improvement	No improvement		
HBO										
Freiberger et al., 2012 [16]	II	G1: HBO (25)	✓	✓	✓	52%	16%	32%	$P = 0{,}203$	Complete healing G1 vs G2
		G2: medical + conservative surgery (21)	✓	✓	✓	33%	5%	62%	P = 0,043*	Improvement G1 vs G2
Freiberger et al., 2007 [68]	V	G1: HBO (16)	N/A	N/A	N/A	44%	50%	6%	P < 0,001	Clinical size (before vs after)
Laser ablation + LLLT										
Atalay et al., 2011 [69]	II	G1: laser ablation + LLLT (10)	✓	✓	✓	70%	30%	–	P = 0,370	Complete healing G1 vs G2
		G2: medical + conservative surgery (10)	✓	✓	✓	40%	60%	–		
Angiero et al., 2009 [70]	III	G1: laser ablation + LLLT (10)	✓	✓	✓	60%	40%	–	N/A	–
		G2: medical (19)	✓	✓	✗	–	74%	26%		
		G3: conservative surgery (20)	✓	✗	✓	–	–	100%		
Vescovi et al., 2012 [50]	III	G1: laser ablation + LLLT (29)	✓	✓	✓	90%	7%	3%	P < 0,0001*	Complete healing G1 vs G2
		G2: medical (28)	✓	✓	✗	18%	7%	75%	P < 0,0001*	Complete healing G2 vs G5
		G3: medical + conservative surgery (17)	✓	✓	✓	65%	–	35%	P = 0,058	Complete healing G3 vs G1
		G4: medical + LLLT (32)	✓	✓	✗	28%	44%	28%	P < 0,0001*	Complete healing G4 vs G1
		G5: medical + conservative surgery + LLLT (33)	✓	✓	✓	73%	9%	18%	P = 0,1161	Complete healing G5 vs G1
Merigo et al., 2018 [17]	V	G1: laser ablation + PRP + LLLT (21)	N/A	✓	✓	95%	5%		N/A	–
LLLT										
Favia et al., 2018 [51]	III	G1: LLLT (21 (24))	✓	✓	✗	–	8%	92%	N/A	–
		G2: medical + conservative surgery (85 (107))	✓	✓	✓	95%	5%	–		
Scoletta et al., 2010 [65]	V	G1: LLLT (20)	N/A	N/A	N/A	20%	40%	40%	P = 0,0034*	Clinical size (before vs after)
Romeo et al., 2011 [52]	V	G1: LLLT + conservative surgery (12)	✓	✓	✗	17%	75%	8%	N/A	–
LPRF										
Park et al., 2017 [24]	I	G1: BMP-2 + LPRF (30)	✓	✓	✓	60%	37%	3%	P = 0,028*	General healing G1 vs G2
		G2: medical + conservative surgery + LPRF (25)	✓	✓	✓	36%	52%	12%		
Giudice et al., 2018 [19]	II	G1: PRF (24)	✓	✓	✓	96%	4%	–	P < 0,05*	Complete healing at 1 m G1 vs G2
		G2: medical + conservative surgery (23)	✓	✓	✓	91%	9%	–		
Coviello et al., 2012 [53]	III	G1: PRP (3)	N/A	✓	✓	100%	–	–	N/A	–
		G3: conservative surgery (4)	N/A	✓	✓	–	50%	50%		
Longo et al., 2014 [54]	III	G1: PRP (34)	✓	✓	✓	94%	6%	–	P = 0,003*	General healing G1 vs G3
		G2: medical (23)	✓	✓	✗	32%	68%	–		
		G3: conservative surgery (15)	✓	✓	✓	53%	47%	–		
Szentpeteri et al., 2020 [67]	III	G1: PRF (73)	N/A	✓	✓	82%	18%	–	P = 0,022*	General healing G1 vs G2
		G2: conservative surgery (28)	N/A	✓	✓	58%	19%	23%	P = 0,005*	Improvement G1 vs G2
Bocanegra-Pérez et al., 2012 [55]	V	G1: LPRP (8)	✓	✓	✓	–	100%	–	N/A	–
Dincă et al., 2014 [56]	V	G1: PRF (10)	✓	✓	✓	100%	–	–	N/A	–
Nørholt et al., 2016 [57]	V	G1: LPRF (15)	✓	✓	✓	93%	–	7%	N/A	–
Mauceri et al., 2018 [58]	V	G1: laser ablation + PRP (10)	✓	✓	✓	30%	50%	20%	P = 0,012*	CH + I at pre-op vs 12 months
Ozone										
Petrucci et al., 2007 [59]	V	G1: ozone (12)	✓	N/A	✓	67%	33%	–	N/A	–
Agrillo et al., 2007 [20]	V	G1: ozone (33)	✓	✓	✓	54%	30%	16%	N/A	–
Agrillo et al., 2012 [60]	V	G1: ozone (94)	✓	✓	✓	60%	30%	10%	P < 0,001*	CH vs I vs NI
Fluorescence guided surgery										
Ristow et al., 2017 [21]	II	G1: auto-fluorescence-guided (20)	✓	✗	✓	90%	–	10%	$P > 0{,}05$	Complete healing G1 vs G2
		G2: tetracycline-fluorescence-guided (20)	✓	✗	✓	85%	–	15%		
Pautke et al., 2011 [61]	V	G1: auto-fluorescence-guided (15 (20))	N/A	✓	✓	85%	15%	0%	N/A	–
Otto et al., 2016 [62]	V	G1: auto-fluorescence-guided (54 (65))	N/A	✓	✓	87%	11%	2%	N/A	–
Teriparatide										
Kim et al., 2014 [64]	III	G1: TPTD + Cal + VitD (15)	N/A	✓	✗	38%	63%	–	P < 0,05*	General healing G1 vs G2
		G2: Cal + VitD (9)	N/A	✓	✗	–	60%	40%		

(*continued on next page*)

Table 2 (*continued*)

Author, year	LOE	Patient groups (n (sites))	AS?	AB?	CS?	HEALING (in general)			Significance	What is significant?
						Complete healing	Improvement	No improvement		
Pelaz et al., 2014 [63]	III	G1: TPTD (4) G2: PRF (5)	N/A N/A	✓ ✓	✗ ✓	25% 100%	50% –	25% –	N/A	–

Table 2: Level of evidence, intervention and control groups, use of antiseptics, antibiotics or conservative surgery, healing outcomes and significance of the included studies. Subdivision based on adjuvant therapies. *LOE* Level of Evidence, *N* number, *AS* Antiseptics, *AB* Antibiotics, *CS* Conservative Surgery, *N/A* Not Available, *G* Group, *HBO* Hyperbaric Oxygenation Therapy, *LLLT* Low Level Laser Therapy, *LPRF* leukocyte-platelet rich fibrin, *CH* Complete Healing, *I* Improvement, *NI* No Improvement.

* Significant $P < 0,05$.

treated with bisphosphonates or denosumab or a combination of both antiresorptive medications [19,21,51,57,62].

The follow-up period ranged from 1 to 39 months. Only 2 studies had a follow-up of less than six months; following the patient sample for 30 days [56] and 3 months [53].

All the patient characteristics are presented in Appendix B. The table is ordered based on the adjuvant treatment and the level of evidence. Number of patients (or sites), the mean age, women/men ratio, primary diagnoses, stage of MRONJ, antiresorptive medication administered, location of the lesion and details on follow up (mean and interval) of the included studies are presented in the table.

Other collected data related to treatment is presented in Table 2. The table is ordered based on the adjuvant treatment and the level of evidence. The patient groups within each article are shown as G1–5. The adjuvant therapy is always group 1 (G1). Some articles use an adjuvant treatment partly or fully as their control groups (G2-G5) [24,50,64]. Info on the use of antiseptics, antibiotics or a conservative surgical approach is given per patient group. The healing outcome (mucosal coverage) is presented. The *P*-values (if available) and if the study results were significant are showed in the last 2 columns.

3.3. Adjuvant therapies

The different adjuvant therapies are discussed in detail in Table 3.

3.3.1. HBO

Freiberger et al. [16,68] studied an HBO therapy after surgical debridement. This adjuvant therapy consisted of 40 sessions at 2.0 atm (atm) for 2 h twice per day.

3.3.2. Laser ablation + LLLT

Atalay et al. [69] performed the debridement with laser ablation technique (Er:YAG; 2940 nm) following LLLT (Nd:YAG; 1064 nm) for 1 min in 5 sessions every two days. Angiero et al. [70] removed necrotic bone with laser ablation (Er:YAG; 2940 nm), subsequently they applied biostimulation with the same device, but with a fifth of the power setting, 3 times for 1 min. In the article of Vescovi et al. [50], the laser ablation (Er:YAG; 2940 nm) was followed by irrigation with povidone iodine solution and LLLT (Nd:YAG; 1064 nm), 5 times for 1 min, once a week for 2 months. Merigo et al. [17] started with piezosurgery to remove the necrotic bone, laser ablation (Er:YAG; 2940 nm) was used until bleeding of the bone. They added platelet rich plasma (PRP; 180 rpm; 10 min) as a gel consistency directly on the wound on a fibrin sponge or with a syringe after suturing, following LLLT (diode laser; 808 nm), 5 times for 1 min, twice a week until suture removal or complete mucosal coverage.

3.3.3. LLLT

Favia et al. [51] reported on LLLT (diode laser; 800 nm) that was applied monthly (they gave no further specifications) without any surgical intervention in the intervention group (G1). Romeo et al. [52] first performed a debridement, following LLLT (double diode laser; 650 nm & 904-910 nm) for 15 min every 3 days for 2 weeks. Scoletta et al. [65] applied LLLT (diode laser; 904 nm) for 15 min in 10 sessions over 20 days, performing a debridement or conservative surgery was not mentioned in the study.

3.3.4. LPRF

Park et al. [24] performed a debridement following application of rhBMP-2 (0.5 ml and a collagen sponge as a carrier) and added L-PRF (3000 rpm; 10 min). Giudice et al. [19] performed a debridement and added PRF (1300 rpm; 8 min). Coviello et al. [53] performed a sequestrectomy and applied PRP as proposed by Marx et al. [71]. Longo et al. [54] performed a debridement and added PRP (firstly 180 rpm for 10 min to separate the erythrocytes, secondly 1800 rpm for 10 min to separate platelet concentrate). Szentpeteri et al. [67] performed a

Table 3
Details on the adjuvant therapy of the included studies.

Author, year	Details on adjuvant therapy
HBO	
Freiberger et al., 2012 [16]	40 HBO treatments at 2.0 ATM for 2 h twice per day
Freiberger et al., 2007 [68]	40 HBO treatments at 2.0 ATM for 2 h twice per day
Laser ablation + LLLT	
Atalay et al., 2011 [69]	Laser ablation (Er:YAG, 2940 nm, 200 mJ) + LLLT (Nd:YAG; 1064 nm) for 1 min, per 2 days, during 5 sessions
Angiero et al., 2009 [70]	Laser ablation (Er:YAG, 2940 nm, 200-250 mJ) + LLLT (Er:YAG, 2940 nm, 50 mJ) 3 times for 1 min
Vescovi et al., 2012 [50]	Laser ablation (Er:YAG; 2940 nm) + irrigation with povidone iodine solution + LLLT (Nd:YAG; 1064 nm) 5 times for 1 min, once a week, for 2 months
Merigo et al., 2018 [17]	Piezotome and Laser Ablation (Er:YAG; 2940 nm, 200 mJ) + PRP (180 rpm; as a gel) + LLLT (diode laser; 808 nm) 5 times for 1 min, twice a week
LLLT	
Favia et al., 2018 [51]	LLLT (800 nm) once a month
Romeo et al., 2011 [52]	LLLT (GaAs, double diode, 650 nm & 904-910 nm) for 15 min, per 3 days, for 2 weeks
Scoletta et al., 2010 [65]	LLLT (GaAs, 904 nm) for 15 min, per 2 days, during 10 sessions
LPRF	
Park et al., 2017 [24]	rhBMP-2 (0,5 ml, collagen sponge as carrier, direct contact with bone) + L-PRF (3000 rpm, 10 min)
Giudice et al., 2018 [19]	PRF (1300 rpm, 8 min)
Coviello et al., 2012 [53]	PRP (as proposed by Marx et al. [71])
Longo et al., 2014 [54]	PRP (180 rpm, 10 min, to separate erythrocytes; 1800 rpm, 10 min, to separate platelet concentrate)
Szentpeteri et al., 2020 [67]	PRF (3000 rpm, 8 min, as membranes, multilayer)
Bocanegra-Pérez et al., 2012 [55]	L-PRP (1 ml thrombin/3 ml plasma, as a gel)
Dincă et al., 2014 [56]	PRF (1300 rpm, 14 min, clots & membranes)
Nørholt et al., 2016 [57]	LPRF (1300 rpm, 14 min, as membranes, multiple layers)
Mauceri et al., 2018 [58]	PRP (180 rpm, 10 min, to separate erythrocytes; 1800 rpm, 10 min, to separate platelet concentrate)
Kim et al., 2014 [66]	LPRF (3000 rpm, 10 min)
Ozone	
Petrucci et al., 2007 [59]	Ozone (7 days pre-operative, 2 sessions during surgery, 7 days post-operative, N/S)
Agrillo et al., 2007 [20]	Ozone (5 cycles of 8 sessions for 3 min, twice a week)
Agrillo et al., 2012 [60]	Ozone (4 cycles of 8 sessions for 3 min, twice a week)
Fluorescence guided surgery	
Ristow et al., 2017 [21]	Preoperative administration of doxycycline (or tetracycline in control group), debridement until a homogenous greenish bone fluorescence was observed using the VELscope system
Pautke et al., 2011 [61]	Preoperative administration of doxycycline, debridement until a homogenous greenish bone fluorescence was observed using the VELscope system
Otto et al., 2016 [62]	Preoperative administration of doxycycline, debridement until a homogenous greenish bone fluorescence was observed using the VELscope system
Teriparatide	
Kim et al., 2014 [64]	Teriparatide (20 μg, once daily, subcutanous selfadministration, maximum 6 months) with Calcium and Vitamin D supplement
Pelaz et al., 2014 [63]	Teriparatide (20 μg, once daily, subcutanous selfadministration, maximum 10 months) vs PRF (vivostat PRF system)
Bovine lactoferrin	
Calvani et al., 2018 [23]	Bovine lactoferrin (100 mg/2 ml, gauze application on surgical site) + bLf tablets (50 mg, locally dissolved, 2 times a day)

Table 3: Details on adjuvant therapy of the included studies, subdivision based on adjuvant therapy. *HBO* Hyperbaric Oxygenation Therapy, *ATM* atmosphere, *Er:YAG* erbium-doped yttrium aluminum garnet, *nm* nanometer, *mJ* microJoule, *LLLT* Low Level Laser Therapy, *Nd:YAG* neodymium-doped yttrium aluminum garnet, *min* minute, *PRP* platelet rich plasma, *rpm* rounds per minute, *GaAs* Gallium arsenide, *LPRF* leukocyte-platelet rich fibrin, *rhBMP-2* recombinant human bone morphogenetic protein-2, *ml* milliliter, *PRF* platelet rich fibrin, *N/S* not specified, *μg* microgram, *bLf* bovine lactoferrin.

debridement and added PRF (3000 rpm; 8 min) as membranes in a multilayer technique. Bocanegra-Pérez et al. [55] performed a debridement and applied L-PRP as a gel (1 ml thrombin/3 ml plasma). Dincă et al. [56] performed a debridement and added LPRF (3000 rpm; 14 min and clot- & membrane-shaped). Nørholt et al. [57] performed a sequestrectomy or a debridement and added LPRF (1300 rpm; 14 min; membrane-shaped; multiple layers). Mauceri et al. [58] performed a debridement with laser ablation (Er,Cr:YSGG; 2780 nm) and applied PRP (firstly 180 rpm for 10 min to separate the erythrocytes, secondly 1800 rpm for 10 min to separate platelet concentrate). Kim et al. [66] performed a debridement and added LPRF (3000 rpm; 10 min) to the wound.

3.3.5. Ozone

Petrucci et al. [59] performed a debridement and applied ozone 7 days pre-operatively, 2 times locally during surgery and 7 days post-operatively (no further details). Agrillo et al. [20,60] performed a debridement and applied ozone in 4 or 5 cycles (pre- and post-operative), each cycle were 8 sessions of ozone therapy, twice a week.

3.3.6. Fluorescence guided surgery

In 2017, Ristow et al. [21] performed a debridement using auto-fluorescence-guided surgery versus tetracycline-fluorescence-guided surgery to identify the better adjuvant therapy among these examples. The VELscope system (VELscope fluorescence lamp; LED Dental, White Rock, British Columbia, Canada) was used for auto-fluorescence. Pautke et al. [61] and Otto et al. [62] only performed a debridement based on auto-fluorescence-guided surgery.

3.3.7. Teriparatide

Pelaz et al. [63] administered only TPTD (subcutane; 20 μg) daily during 4 to 10 months as intervention. The control group had a debridement combined with application of PRF (no further details). Kim et al. [64] administered TPTD (subcutane; 20 μg) daily during 6 months and added Calcium and Vitamin D supplementation.

3.3.8. Bovine Lactoferrin

Calvani et al. [23] performed a debridement and applied bLf (100 mg/2 ml, gauze application, 10 min) combined with tablets of bLf (at home, tablets locally dissolved, 50 mg, 2×/day). The control group

had application of sterile gauzes combined with the same tablets as the intervention group.

Two articles [23,66] included in this systematic review but absent in Table 2, presented their results differently from the majority of the papers. Kim et al. [66] presented the results of their LPRF study based on mucosal coverage over time instead of a fixed follow-up period. Seventy-seven percent had a complete resolution (mucosal coverage at 1 month), 18% had a delayed resolution (mucosal coverage between 1 and 4 months) and 6% had no resolution (persistence of the lesion at 4 month follow-up). There was a significant association between response to treatment and stage of MRONJ ($p = 0.002$); the higher the stage of MRONJ, the worse the response to treatment. All patients in the study of Calvani et al. [23] on bLf had mucosal coverage, but obtained this point of healing at different levels of the follow up. The intervention group had 31% and 100% complete healing at 1 and 2 weeks. The control group had 15% and 100% complete healing at 2 and 3 months respectively.

3.4. Risk of bias within studies

The Newcastle-Ottawa Scale [31,32] was used to determine the risk of bias for the included studies. Table 4 provides a breakdown of the components of this bias tool.

4. Discussion

The purpose of this study was to give an overview of all existing adjuvant therapies for treating MRONJ and the evaluate the effectiveness and the differences in outcome of these therapies. Publications on this matter have greatly increased the last decade since MRONJ is a recently discovered pathology [2].

Performing a meta-analysis on the subject appeared impossible because of the high variation in study designs, protocols and reports on outcome [72]. Additionally, the majority of the included articles had a medium to high risk of bias, so that results should be interpreted with caution. This systematic review was not limited to only RCTs to present a complete review of the literature.

Based on this review, we can cautiously state the following regarding the adjuvant therapies.

HBO therapy showed a significantly improved healing based on a RCT with a low risk of bias [16]. Yet clinical success seems rather low (44–52% complete healing) and no further research has been conducted on HBO therapy.

The combination of Laser Ablation and LLLT gave a success of 60–95% for complete healing. Yet, it might be that the success is rather related to laser ablation alone or surgical treatment in general. Indeed, a non-randomized study concluded that LLLT is inferior to a surgical approach [51] which was confirmed by other articles using only LLLT, reporting complete healing with only 0–20% of the patients [51,52,65]. Vescovi et al. [50] used several control groups, with a conservative or a surgical approach, and showed that minimal invasive surgery had the best healing results in the general population of MRONJ. A subdivision based on MRONJ stages was not reported. Unfortunately, this article had a high risk of bias according to the NOS scale.

The first report of treating MRONJ with platelet derived growth factors was published in 2007 [73]. The overall success of LPRF as an adjuvant treatment may be due to the surgical component since all interventions were combined with a surgical approach. Longo et al. [54] and Szentpeteri et al. [67] stated a significant difference in healing between the LPRF group and the control group. However, both studies had a medium risk of bias. Giudice et al. could only show a significant difference between L-PRF and control at one month of follow-up [19]. This study results are trustworthy given the low risk of bias and the randomized controlled trial design. LPRF might thus be useful to fasten the healing process. The reason for this might be that L-PRF acts as a membrane, thus avoiding direct contact between bone and oral mucosa [57,74,75]. The use of adjuvant BMP may even enhance healing because of its osteoconductive effects [24,76,77].

Regarding ozone therapy, none of the reported studies had a control group and all of them had a medium to high risk of bias. A reserved interpretation is certainly appropriate given that there are no controlled papers published yet on this subject.

Fluorescence-guided bone surgery is a way to objectify the surgeon's intraoperative control of the transition of necrotic to vital bone and thereby standardizes the technique. This can limit the MRONJ resection to a minimum and optimize the healing process as such. No significant difference was reported between the auto-fluorescence-guided and tetracycline-fluorescence-guided surgery [21]. No study compared the fluorescence-guided surgery to standard surgery techniques.

Literature on teriparatide is scarce. Only two articles with a non-surgical intervention group were identified [63,64]. The complete healing outcome was low (25–38%), with selection bias further lowering the clinical evidence. Both articles only included osteoporosis cases, with MRONJ stages II and III.

As to lactoferrin as adjuvant treatment option for MRONJ. According to Calvani et al. [23] the difference in the healing time when using lactoferrin versus conservative medical therapy was a few weeks and up to three months respectively. More research on this matter is recommended to promote this adjuvant treatment.

More adjuvant therapies, such as pentoxifylline and tocopherol [27,78], geranylgeraniol [25,79] or BMP alone [80], are reported in literature, but these articles did not meet the inclusion criteria. Further, therapies that might gain importance in the future aremesenchymal stem cells (MSCs) [26,81], the use of dental pulp MSCs [82] and the use of human amniotic membrane [83].

It is difficult to draw firm conclusions from this systematic review. The adjuvant therapy is often combined with either the standard surgical or medical conservative treatment. Both approaches can influence the result and thus be a confounding factor with respect to each other. For this reason, the results in this systematic review must be interpreted with the necessary precautions.

As stated above, the heterogeneity, lack of control group in some of the studies and the high number of articles with a medium to high risk of bias also limit the conclusions that can be drawn of this systematic review. Most of the articles were non-randomized retrospective studies which make the articles susceptible for all forms of bias. Combining data of heterogeneous articles can be misleading so that wrong conclusions could be drawn. A statement could be made to standardize the outcome measures since comparing the results of different experimental treatments is often impossible to a high variety of parameters. To evaluate the effectiveness of an adjuvant treatment more well-controlled studies are necessary. Some of the included articles had a major discrepancy in treatment of the intervention and control groups [51,63]. It is evident that in further studies, a medical or surgical adjuvant treatment should always be compared to either a standard medical or surgical therapy respectively to minimize the intrinsic difference in the results between a medical and surgical therapy.

5. Conclusions

The results of this systematic review suggest that an adjuvant therapy concomitant with the standard surgical or medical conservative approach may offer an advantage to a standard surgical or medical conservative approach solely. Yet, the present outcomes should be interpreted cautiously because of bias and low evidence study designs. There seem to be some indications that laser ablation, LPRF and fluorescence guided surgery might present interesting options for treating MRONJ. There is an urgent need for conducting more randomized well-controlled trials before implementing these adjuvant therapies in a standard treatment protocol of MRONJ.

Table 4
Newcastle-Ottawa Quality Assessment.

Author, year	Representativeness of the intervention cohort	Selection of the non-intervention cohort	Ascertainment of intervention	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	Stars (n)	Overall risk of bias
HBO										
Freiberger et al., 2012 [16]	Low (★)	Low (★)	Low (★)	Yes (★)	High: no control of potential confounding variable	High: assessment done by the study's surgeon	Yes (★)	Loss < 20% (★)	6	Low
Freiberger et al., 2007 [68]	High: no MRONJ staging	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Laser ablation + LLLT										
Atalay et al., 2011 [69]	High: mostly stage II ONJ	Low (★)	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	5	Medium
Angiero et al., 2009 [70]	High: no MRONJ staging	High: no MRONJ staging	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Loss < 20% (★)	4	Medium
Vescovi et al., 2012 [50]	High: only staging, no further information	High: only staging, no further information	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Unclear: no discription	Unclear: no discription	2	High
Merigo et al., 2018 [17]	Low (★)	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	5	Medium
LLLT										
Favia et al., 2018 [51]	High: treatment based on general health	Low (★)	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	5	Medium
Scoletta et al., 2010 [65]	Low (★)	N/A	Low (★)	Yes (★)	N/A	Low: Single skilled examiner (★)	Yes (★)	Complete follow up (★)	6	Low
Romeo et al., 2011 [52]	Low (★)	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	complete follow up (★)	5	Medium
LPRF										
Park et al., 2017 [24]	Low (★)	Low (★)	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	yes (★)	Complete follow up (★)	6	Low
Giudice et al., 2018 [19]	Low (★)	Low (★)	Low (★)	Yes (★)	High: no control of potential confounding variable	Low: same indepedent resident (★)	Yes (★)	Complete follow up (★)	7	Low
Coviello et al., 2012 [53]	High: no MRONJ staging	High: no MRONJ staging	Low (★)	Yes (★)	High: no control of potential confounding variable	Low: same calibrated examiner (★)	No: only 3 months	complete follow up (★)	4	Medium
Longo et al., 2014 [54]	High: surgical treatment if medical therapy was insufficient	High: surgical treatment if medical therapy was insufficient	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	5	Medium
Szentpeteri et al., 2020 [67]	High: only stage II or III	High: based on the duration of treatment	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Bocanegra-Pérez et al., 2012 [55]	High: only stage II MRONJ	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Dincă et al., 2014 [56]	High: only stage II MRONJ	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	No: only 30 days	Complete follow up (★)	3	High

(*continued on next page*)

Table 4 (*continued*)

Author, year	Representativeness of the intervention cohort	Selection of the non-intervention cohort	Ascertainment of intervention	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	Stars (n)	Overall risk of bias
Nørholt et al., 2016 [57]	High: only stage II or III and intervention after failure of medical therapy	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Mauceri et al., 2018 [58]	High: only stage I & II	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Kim et al., 2014 [66]	High: only women (★)	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	5	Medium
Ozone										
Petrucci et al., 2007 [59]	High: no MRONJ staging	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Unclear: no discription	Complete follow up (★)	3	High
Agrillo et al., 2007 [20]	High: no MRONJ staging	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Agrillo et al., 2012 [60]	High: no MRONJ staging	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Fluorescence guided surgery										
Ristow et al., 2017 [21]	Low (★)	Low (★)	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	6	Low
Pautke et al., 2011 [61]	High: stage II and III MRONJ	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	Unclear: no discription; preliminary results	Complete follow up (★)	3	High
Otto et al., 2016 [62]	Low (★)	N/A	Low (★)	Yes (★)	N/A	Unclear: no discription	yes (★)	Complete follow up (★)	5	Medium
Teriparatide										
Kim et al., 2014 [64]	High: only osteoporisis, stage II and III MRONJ	High: only osteoporisis, stage II and III MRONJ, refusing TPTD treatment (repulsing to self-injection)	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Pelaz et al., 2013 [63]	High: no surgery possible due general condition	High: previous surgeries with adverse outcome	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium
Bovine Lactoferrin										
Calvani et al., 2018 [23]	High: only stage II ONJ, only carcinomas as primary diagnoses	High: previous surgeries with adverse outcome	Low (★)	Yes (★)	High: no control of potential confounding variable	Unclear: no discription	Yes (★)	Complete follow up (★)	4	Medium

Table 4: Newcastle-Ottawa Quality Assessment Scale for included studies.

Declaration of competing interest

None.

Funding

None.

Acknowledgements

None.

Appendix A

The search strategy used for Pubmed: ("Osteonecrosis"[Mesh] OR Osteonecros*[tiab] OR "Bisphosphonate-Associated Osteonecrosis of the Jaw"[Mesh] OR ONJ[tiab] OR BRONJ[tiab] OR MRONJ[tiab] OR ARONJ[tiab]) AND ("Jaw"[Mesh] OR Jaw*[tiab] OR Alveolar process*[tiab] OR tooth socket*[tiab] OR dental arch*[tiab] OR mandible[tiab] OR maxilla[tiab] OR palate[tiab]) ((("Therapeutics"[Mesh] OR "Disease Management"[Mesh] OR Treatment*[tiab] OR Therap*[tiab] OR Disease Management[tiab]) AND (new[tiab] OR novel[tiab] OR alternative[tiab] OR modern[tiab] OR recent[tiab] OR complementary[tiab] OR supplementary[tiab] OR adjuvant[tiab] OR accessory[tiab] OR additional[tiab])) OR "complementary therapies"[MeSH] OR "Biological Control Agents"[Mesh] OR Biological molecule*[tiab] OR bFGF[tiab] OR BMP*[tiab] OR LPRF [tiab] OR PRP[tiab] OR APC[tiab] OR PDGF[tiab] OR PRGF[tiab] OR PRF[tiab] OR PRT[tiab] OR "platelet-rich plasma"[tiab] OR "platelet rich plasma"[tiab] OR "platelet concentrate*"[tiab] OR "Platelet-derived growth factor*"[tiab] OR "Platelet derived growth factor*"[tiab] OR "platelet-rich growth factor*"[tiab] OR "platelet rich growth factor*"[tiab] OR "platelet-rich fibrin"[tiab] OR "platelet rich fibrin"[tiab] OR "leukocyte- and platelet-rich fibrin"[tiab] OR "leukocyte and platelet rich fibrin"[tiab] OR "autologous platelet concentrate"[tiab] OR "Platelet-rich therap*"[tiab] OR "Platelet rich therap*"[tiab] OR "Pentoxifylline"[Mesh] OR Pentoxifylline[tiab] OR Oxpentifylline[tiab] OR "Tocopherols"[Mesh] OR Tocopherol*[tiab] OR "Ultrasonic Therapy"[Mesh] OR "Ultrasound therap*" OR "Ultrasonic therap*"[tiab] OR "Low-Level Light Therapy"[Mesh] OR "Low-Level Light Therapy"[tiab] OR "Low Level Light Therapy"[tiab] OR "Low-level laser therapy"[tiab] OR "Low level laser therapy"[tiab] OR LLLT[tiab] OR "Osteogenesis, Distraction"[Mesh] OR "Distraction osteogenesis"[tiab] OR "Ozone"[Mesh] OR Ozone[tiab] OR trioxygen[tiab] OR "geranylgeraniol" [Supplementary Concept] OR geranylgeraniol[tiab] OR lactoferrin[tiab] OR lactotransferrin[tiab] OR "Hyperbaric Oxygenation"[Mesh] OR "Hyperbaric oxygen*"[tiab] OR HBO[tiab]).

Appendix B

Details on the included studies. Level of evidence (LOE), details of the patient characteristics (number of patients (sites), mean age, women/men ratio, primary diagnoses, stages of MRONJ, antiresorptive medication administered, location of the lesion) and details on follow-up (mean and interval) of the included studies.

Author, year	LOE	Patients (sites)	Mean age	Women/men ratio (%)	Primary diagnoses	Stages MRONJ	Antiresorptive medication	Location	Follow-up	Follow-up interval
HBO										
Freiberger et al., 2012 [16]	II	46	66,2y	57,2%/ 42,8%	MM (39,6%) BreastCa (25%) Other (20,4%) Osteoporosis (14,6%)	All stages (N/S)	BP (100%)	N/A	2y	3;6;12;18;24 m
Freiberger et al., 2007 [68]	V	16	N/A	37,5%/ 62,5%	MM (62,5%) BreastCa (18,8%) ProstateCa (6,3%) Sarcoidosis (6,3%) Waldenstrom's macro-globulinemia (6,3%)	N/A	BP (100%)	Man (75%) Max (12,5%) Both (12,5%)	1 m to 24 m	post-HBO; any visit with relapse; at least 1 m after therapy
Laser ablation + LLLT										
Atalay et al., 2011 [69]	II	20	55,4y	65%/35%	MM (55%) BreastCa (35%) ProstateCa (5%) NET (5%)	Stage I (30%) Stage II (70%)	BP (100%)	Man (45%) Max (55%)	6 months	2;4;6;8;10d, 1;2;3;4;5;6 m
Angiero et al., 2009 [70]	III	49	69,8y	67,3%/ 32,7%	MM (57,1%) BreastCa (16,3%) ProstateCa (4,1%) RenalCa (4,1%) LaryngCa (2,0%) Paget (4,1%) LungCa (4,1%) Osteoporosis (8,2%)	Stage I (2%) Stage II (N/S) Stage III (N/S)	BP (100%)	Man (77,6%) Max (22,4%)	39 m (mean)	N/A
Vescovi et al., 2012 [50]	III	151 (139)	66,9y	72,8%/ 27,2%	MM (37,1%) Bone metastasis (43%) Osteoporosis (19,9%)	Stage I (15,9%) Stage II (67,5%) Stage III (16,6%)	BP (100%)	Man (62,9%) Max (27,8%) Both (9,3%)	N/A	N/A

Merigo et al., 2018 [17]	V	21	72,6y	76,2%/ 23,8%	BreastCa (33,3%) ProstateCa (9,5%) PancreasCa (4,8%) RenalCa (4,8%) Reu Art (4,8%) Osteoporosis (42,9%)	Stage I (9,6%) Stage II (71,4%) Stage III (19%)	BP (100%)	Man (71,4%) Max (28,6%)	9,6 m (mean)	N/A
LLLT										
Favia et al., 2018 [51]	III	106 (131)	70,4y	69,8%/ 30,2%	Oncologic (72,5%) Non-oncologic (27,5%)	Stage I (8,4%) Stage II (49,6%) Stage III (42%)	BP (79,2%) Denosumab (15,4%) Both (5,4%)	Man (64,9%) Max (35,1%)	18 m (mean)	1;2;3;4w, 3;6;12 m
Romeo et al., 2011 [52]	V	12	62y	58%/42%	MM (33,4%) BreastCa (25%) ProstateCa (25%) LungCa (8,3%) Osteoporosis (8,3%)	Stage I (16,7%) Stage II (66,6%) Stage III (16,7%)	BP (100%)	Man (83,4%) Max (8,3%) Both (8,3%)	6 m	1;2;3;4;5;6 m
Scoletta et al., 2010 [65]	V	20	71,3y	70%/30%	MM (30%) BreastCa (30%) ProstateCa (15%) Osteoporosis (25%)	Stage I (10%) Stage II (80%) Stage III (10%)	BP (100%)	N/A	8 m (mean)	1;2;3;6;9;12;15 m; every 3 m further one
LPRF										
Park et al., 2017 [24]	I	55	75,2y	93%/7%	Bone metastasis (12,7%) Osteoporosis (87,3%)	Stage I (14,5%) Stage II (78,2%) Stage III (7,3%)	BP (100%)	Man (67,3%) Max (29,1%) Both (3,6%)	10 m (mean)	1;2;3;4w, 2;3;4;5;6 m
Giudice et al., 2018 [19]	II	47	74,7y	51%/49%	MM (2,1%) BreastCa (23,4%) ProstateCa (31,9%) RenalCa (10,6%) LungCa (6,4%) Osteoporosis (25,5%)	Stage II (57,4%) Stage III (42,6%)	BP (78,7%) Denosumab (21,3%)	Man (74,5%) Max (10,6%) Both (14,9%)	1 year	1;6 m, 1y
Coviello et al., 2012 [53]	III	7	75,6y	71,4%/ 28,6%	MM (100%)	N/A	BP (100%)	Man (71,4%) Max (0%) Both (28,6%)	3 m	15d, 1;2;3 m
Longo et al., 2014 [54]	III	72	59y	83,3%/ 16,7%	MM (1,4%) BreastCa (75%) ProstateCa (12,5%) LungCa (11,1%)	Stage 0 (6,9%) Stage I (15,3%) Stage II (56,9%) Stage III (20,8%)	BP (100%)	N/A	6 m to 94 m	Regular follow-up (N/S)
Szentpeteri et al., 2020 [67]	III	101	65,9y	73,3%/ 26,7%	MM (11,9%) BreastCa (40,6%) ProstateCa (17,8%) RenalCa (3,0%) Other (11,9%) Osteoporosis (14,9%)	Stage II (76,2%) Stage III (23,8%)	BP (100%)	Man (67,3%) Max (26,7%) NA (5,9%)	1y	1;2w, 1;3;6;12 m
Bocanegra-Pérez et al., 2012 [55]	V	8	66y	75%/25%	MM (50%) BreastCa (25%) Osteoporosis (25%)	Stage II (100%)	BP (100%)	Man (87,5%) Max (12,5%)	14 m (mean)	2;4;6;10;14w
Dincă et al., 2014 [56]	V	10	59y	60%/40%	MM (20%) BreastCa (30%) ProstateCa (30%) RenalCa (10%) BowelCa (10%)	Stage II (100%)	BP (100%)	Man (70%); Max (30%)	30d	3;5;10;30d
Nørholt et al., 2016 [57]	V	15	68,5y	73%/27%	MM (6,7%) BreastCa (26,7%) ProstateCa (6,7%) RenalCa (13,3%) Osteoporosis (46,7%)	Stage II (86,7%) Stage III (13,3%)	BP (73,3%) Denosumab (26,7%)	Man (73,3%) Max (20%) Both (6,7%)	7 m to 20 m	At least 6 m
Mauceri et al., 2018 [58]	V	10	75,2y	70%/30%	MM (40%) BreastCa (30%) ProstateCa (30%)	Stage I (60%) Stage II (40%)	BP (100%)	Man (90%) Max (10%)	12 m	15d, 1;3;6;12 m

Kim et al., 2014 [-66]	V	34	71y	100%/0%	Bone metastasis (5,9%) Osteoporosis (94,1%)	Stage I (20,6%) Stage II (61,8%) Stage III (17,6%)	BP (100%)	Man (79,4%) Max (20,6%)	6 m	1;2;3;4;5;6w, 2;3;4;5;6 m
Ozone										
Petrucci et al., 2007 [59]	V	12	72y	75%/25%	MM (100%)	N/A	BP (100%)	NA	N/A	N/A
Agrillo et al., 2007 [20]	V	33	64y	67,2%/ 32,8%	MM (65,6%) BreastCa (27,6%) ProstateCa (1,7%) RenalCa (1,7%) BladderCa (1,7%) Rheu Art (1,7%)	N/A	BP (100%)	Man (55%) Max (28%) Both (17%)	7 m	N/A
Agrillo et al., 2012 [60]	V	94	57y	62,8%/ 37,2%	MM (43,3%) BreastCa (31,5%) ProstateCa (5,5%) RenalCa (6,3%) LungCa (7,9%) Osteoporosis & other (5,5%)	N/A	BP (100%)	Man (55%) Max (33%) Both (12%)	6,5 m	N/A
Fluorescence guided surgery										
Ristow et al., 2017 [21]	II	40 (51)	71,8y	65%/35%	MM (10%) BreastCa (45%) ProstateCa (25%) RenalCa (2,5%) LiverCa (2,5%) Osteoporosis (15%)	Stage I (7,8%) Stage II (80,4%) Stage III (11,8%)	BP (80%) Denosumab (0%) Both (20%)	Man (64,7%) Max (35,3%)	1y	10d, 8w, 6 m, 1y
Pautke et al., 2011 [61]	V	15 (20)	63,2y	66,7%/ 33,3%	MM (26,7%) BreastCa (53,3%) ProstCa (20%)	Stage II (75%) Stage III (25%)	BP (100%)	Man (65%) Max (35%)	4w	2;4w, every 3 m further on
Otto et al., 2016 [62]	V	54 (65)	71,4y	59,3%/ 40,7%	MM (7,4%) BreastCa (37%) ProstateCa (29,6%) ThyroidCa (3,7%) SquamousCellCa (1,9%) BronchialCa (1,9%) EndometrialCa (1,9%) Osteoporosis (16,7%)	Stage 0 (1,5%) Stage I (21,5%) Stage II (64,6%) Stage III (12,3%)	BP (87%) Denosumab (5,6%) Both (7,4%)	Man (61,5%) Max (38,5%)	12,9 m (mean)	1;2;3;4w, 2;3;4;5;6;7;8;9;10;11;12 m
Teriparatide										
Kim et al., 2014 [-64]	III	24	75,9y	91,7%/8,3%	Osteoporosis (100%)	Stage II (91,7%) Stage III (8,3%)	BP (100%)	Man (70,8%) Max (29,2%)	6 m	1;3;6 m
Pelaz et al., 2014 [63]	III	9	73,2y	100%/0%	Osteoporosis (100%)	NA	BP (100%)	Man (88,9) Max (11,1%)	16,6 m (mean)	15;30;45;60;75;90d
Bovine lactoferrin										
Calvani et al., 2018 [23]	III	26	N/A	80,8%/ 19,2%	BreastCa (73,1%) ProstateCa (11,5%) LungCa (7,7%) LiverCa (7,7%)	Stage II (100%)	BP (100%)	N/A	6 m	1;2;3;4d, 1;2;4;8;12w, 6;12;24 m

Appendix A: Level of evidence (LOE), details of the patient characteristics (number of patients (sites), mean age, women/men ratio, primary diagnoses, stages of MRONJ, antiresorptive medication administered, location of the lesion) and details on follow-up (mean and interval) of the included studies. Subdivision based on complemntary therapy. *HBO* Hyperbaric Oxygenation Therapy, *LLLT* Low Level Laser Therapy, *LPRF* leukocyte-platelet rich fibrin, *N/A* Not available, *N/S* Not specified, *MM* Multiple Myeloma, *Ca* Carcinoma, *NET* Neuro Endocrine Tumor, *Reu Art* Reumathoid Artritis, *BP* Bisphosphonates, *Man* Mandible, *Max* Maxilla, *d* Days, *w* Weeks, *m* Months, *y* Year.

References

[1] Clézardin P. Mechanisms of action of bisphosphonates in oncology: a scientific concept evolving from antiresorptive to anticancer activities. Bonekey Rep [Internet]. 2013;2(267):1–7. Available from: doi:https://doi.org/10.1038/bonekey.2013.1.

[2] Marx RE. Pamidronate (Aredia) and Zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg [Internet]. 2003;61:1115–7. Available from: doi:https://doi.org/10.1016/s0278-2391(03)00720-1.

[3] Ruggiero SL, Mehrotra B, Rosenberg TJ, Engroff SL. Osteonecrosis of the jaws associated with the use of bisphosphonates: a review of 63 cases. J Oral Maxillofac Surg [Internet]. 2004;62(5):527–34. Available from: doi:https://doi.org/10.1016/j.joms.2004.02.004.

[4] Hellstein JW, Marek CL. Bisphosphonate osteochemonecrosis (bis-phossy jaw): Is this phossy jaw of the 21st century? J Oral Maxillofac Surg [Internet]. 2005;63(5):682–9. Available from: doi:https://doi.org/10.1016/j.joms.2005.01.010.

[5] Ruggiero SL, Dodson TB, Assael LA, Landesberg R, Marx RE, Mehrotra B. American association of oral and maxillofacial surgeons position paper on bisphosphonate-related osteonecrosis of the jaw - 2009 update. J Oral Maxillofac Surg [Internet]. 2009;67(5 Suppl):2–12. Available from: doi:https://doi.org/10.1016/j.joms.2009.01.009.

[6] Aghaloo TL, Felsenfeld AL, Tetradis S. Osteonecrosis of the jaw in a patient on denosumab. J Oral Maxillofac Surg [Internet]. 2010;68(5):959–63. Available from: doi:https://doi.org/10.1016/j.joms.2009.10.010.

[7] Kyrgidis A, Toulis KA. Denosumab-related osteonecrosis of the jaw. Osteoporos Int [Internet]. 2011;22(1):369–70. Available from: doi:https://doi.org/10.1007/s00198-010-1177-6.

[8] Santos-Silva AR, Belizario Rosa GA, Castro Junior G de, Dias RB, Prado Ribeiro AC, Brandao TB. Osteonecrosis of the mandible associated with bevacizumab therapy. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2013 Jun;115(6):e32-6. Available from: doi:https://doi.org/10.1016/j.oooo.2013.02.001.

[9] Ramírez L, López-Pintor RM, Casañas E, Arriba L de, Hernández G. New non-Bisphosphonate drugs that produce osteonecrosis of the jaws. Oral Health Prev Dent [Internet]. 2015;13(5):385–93. Available from: doi:https://doi.org/10.3290/j.ohpd.a34055.

[10] Brunello A, Saia G, Bedogni A, Scaglione D, Basso U. Worsening of osteonecrosis of the jaw during treatment with sunitinib in a patient with metastatic renal cell carcinoma. Bone [Internet]. 2009 Jan;44(1):173–5. Available from: doi:https://doi.org/10.1016/j.bone.2008.08.132.

[11] Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, et al. American association of oral and maxillofacial surgeons position paper on medication-related osteonecrosis of the jaw - 2014 update. J Oral Maxillofac Surg [Internet]. 2014;72(10):1938–56. Available from: doi:https://doi.org/10.1016/j.joms.2014.04.031.

[12] Fliefel R, Troltzsch M, Kuhnisch J, Ehrenfeld M, Otto S. Treatment strategies and outcomes of bisphosphonate-related osteonecrosis of the jaw (BRONJ) with characterization of patients: a systematic review. Int J Oral Maxillofac Surg [Internet]. 2015 May;44(5):568–85. Available from: doi:https://doi.org/10.1016/j.ijom.2015.01.026.

[13] El-Rabbany M, Sgro A, Lam DK, Shah PS, Azarpazhooh A. Effectiveness of treatments for medication-related osteonecrosis of the jaw: a systematic review and meta-analysis. J Am Dent Assoc [Internet]. 2017 Aug;148(8):584-594.e2. Available from: doi:https://doi.org/10.1016/j.adaj.2017.04.002.

[14] Rupel K, Ottaviani G, Gobbo M, Contardo L, Tirelli G, Vescovi P, et al. A systematic review of therapeutical approaches in bisphosphonates-related osteonecrosis of the jaw (BRONJ). Oral Oncol [Internet]. 2014 Nov;50(11):1049–57. Available from: doi:https://doi.org/10.1016/j.oraloncology.2014.08.016.

[15] de Souza Tolentino E, de Castro TF, Michellon FC, Passoni ACC, Ortega LJA, Iwaki LCV, et al. Adjuvant therapies in the management of medication-related osteonecrosis of the jaws: systematic review. Head Neck [Internet]. 2019;41(12):4209–28. Available from: doi:https://doi.org/10.1002/hed.25944.

[16] Freiberger JJ, Padilla-Burgos R, McGraw T, Suliman HB, Kraft KH, Stolp BW, et al. What is the role of hyperbaric oxygen in the management of bisphosphonate-related osteonecrosis of the jaw: a randomized controlled trial of hyperbaric oxygen as an adjunct to surgery and antibiotics. J Oral Maxillofac Surg [Internet]. 2012;70(7):1573-1583. Available from: doi:https://doi.org/10.1016/j.joms.2012.04.001.

[17] Merigo E, Cella L, Oppici A, Cristina Arbasi M, Clini F, Fontana M, et al. Combined approach to treat medication-related osteonecrosis of the jaws. J Lasers Med Sci [Internet]. 2018;9(2):92–100. Available from: doi:10.15171/jlms.2018.19.

[18] Karu T. Is it time to consider photobiomodulation as a drug equivalent? Photomed Laser Surg [Internet]. 2013;31(5):189–91. Available from: doi:https://doi.org/10.1089/pho.2013.3510.

[19] Giudice A, Barone S, Giudice C, Bennardo F, Fortunato L. Can platelet-rich fibrin improve healing after surgical treatment of medication-related osteonecrosis of the jaw? A pilot study. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2018;126(5):390–403. Available from: doi:https://doi.org/10.1016/j.oooo.2018.06.007.

[20] Agrillo A, Ungari C, Filiaci F, Priore P, Iannetti G. Ozone therapy in the treatment of avascular bisphosphonate-related jaw osteonecrosis. J Craniofac Surg [Internet]. 2007 Sep;18(5):1071–5. Available from: doi:https://doi.org/10.1097/scs.0b013e31857261f.

[21] Ristow O, Otto S, Geiss C, Kehl V, Berger M, Troeltzsch M, et al. Comparison of autofluorescence and tetracycline fluorescence for guided bone surgery of medication-related osteonecrosis of the jaw: a randomized controlled feasibility study. Int J Oral Maxillofac Surg [Internet]. 2017 Feb;46(2):157–66. Available from: doi:https://doi.org/10.1016/j.ijom.2016.10.008.

[22] Rubin MR, Bilezikian JP. The anabolic effects of parathyroid hormone therapy. Clin Geriatr Med [Internet]. 2003;19(2):415–32. Available from: doi:https://doi.org/10.1016/s0749-0690(02)00074-5.

[23] Calvani F, Cutone A, Lepanto MS, Rosa L, Valentini V, Valenti P. Efficacy of bovine lactoferrin in the post-surgical treatment of patients suffering from bisphosphonate-related osteonecrosis of the jaws: an open-label study. BioMetals [Internet]. 2018 Feb;31(3):445–55. Available from: doi:https://doi.org/10.1007/s10534-018-0081-y.

[24] Park J-HH, Kim J-WW, Kim S-JJ. Does the addition of bone morphogenetic protein 2 to platelet-rich fibrin improve healing after treatment for medication-related osteonecrosis of the jaw? J Oral Maxillofac Surg [Internet]. 2017 Jun;75(6):1176–84. Available from: doi:https://doi.org/10.1016/j.joms.2016.12.005.

[25] Ziebart T, Koch F, Klein MO, Guth J, Adler J, Pabst A, et al. Geranylgeraniol - a new potential therapeutic approach to bisphosphonate associated osteonecrosis of the jaw. Oral Oncol [Internet]. 2011 Mar;47(3):195–201. Available from: doi:https://doi.org/10.1016/j.oraloncology.2010.12.003.

[26] Voss PJ, Matsumoto A, Alvarado E, Schmelzeisen R, Duttenhofer F, Poxleitner P. Treatment of stage II medication-related osteonecrosis of the jaw with necrosectomy and autologous bone marrow mesenchymal stem cells. Odontology [Internet]. 2017 Oct;105(4):484–93. Available from: doi:https://doi.org/10.1007/s10266-017-0295-4.

[27] Owosho AA, Estilo CL, Huryn JM, Yom SK. Pentoxifylline and tocopherol in the management of cancer patients with medication-related osteonecrosis of the jaw: an observational retrospective study of initial case series. Oral Surg Oral Med Oral Pathol Oral Radiol [Internet]. 2016 Oct;122(4):455–9. Available from: doi:https://doi.org/10.1016/j.oooo.2016.06.019.

[28] Higgins J, Altman D. Chapter 8: assessing risk of bias in included studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). Higgins J, Green S, editors. The Cochrane Collaboration; 2011.

[29] Cochrane and Systematic Reviews: Relevance of the Evidence [Internet]. [cited 2019 Apr 18]. Available from: http://consumers.cochrane.org/cochrane-and-systematic-reviews.

[30] Oxman A. Checklists for review articles. Br Med J [Internet]. 1994;309(6955):648–51. Available from: doi:https://doi.org/10.1136/bmj.309.6955.648.

[31] Wells G, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. 2015 [cited 2019 Apr 18]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.

[32] Reeves B, Deeks J. Chapter 13: including non-randomized studies. In: Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 (Updated March 2011). Higgins J, Green S, editors. The Cochrane Collaboration; 2011.

[33] Agrillo A, Petrucci MT, Tedaldi M, Mustazza MC, Marino SMF, Gallucci C, et al. New therapeutic protocol in the treatment of avascular necrosis of the jaws. J Craniofac Surg [Internet]. 2006 Nov;17(6):1080–3. Available from: doi:https://doi.org/10.1097/01.scs.0000249350.59096.d0.

[34] Vescovi P, Merigo E, Meleti M, Fornaini C, Nammour S, Manfredi M. Nd:YAG laser biostimulation of bisphosphonate-associated necrosis of the jawbone with and without surgical treatment. Br J Oral Maxillofac Surg [Internet]. 2007 Dec;45(8):628–32. Available from: doi:https://doi.org/10.1016/j.bjoms.2007.03.016.

[35] Fleisher KE, Pham S, Raad RA, Friedman KP, Ghesani M, Chan KC, et al. Does fluorodeoxyglucose positron emission tomography with computed tomography facilitate treatment of medication-related osteonecrosis of the jaw? J Oral Maxillofac Surg [Internet]. 2016;74(5):945–58. Available from: doi:https://doi.org/10.1016/j.joms.2015.10.025.

[36] Mücke T, Koerdt S, Jung M, Mitchell DA, Wolff KD, Kesting MR, et al. The role of mylohyoid flap in the treatment of bisphosphonate-related osteonecrosis of the jaws. J Cranio-Maxillofacial Surg [Internet]. 2016;44(4):369–73. Available from: doi:https://doi.org/10.1016/j.jcms.2015.12.017.

[37] Jung J, Yoo H-Y, Kim G-T, Lee J-W, Lee Y-A, Kim D-Y, et al. Short-term teriparatide and recombinant human bone morphogenetic protein-2 for regenerative approach to medication-related osteonecrosis of the jaw: a preliminary study. J Bone Miner Res [Internet]. 2017 Dec;32(12):2445–52. Available from: doi:https://doi.org/10.1002/jbmr.3237.

[38] Asaka T, Ohga N, Yamazaki Y, Sato J, Satoh C, Kitagawa Y. Platelet-rich fibrin may reduce the risk of delayed recovery in tooth-extracted patients undergoing oral bisphosphonate therapy: a trial study. Clin Oral Investig [Internet]. 2017 Sep;21(7):2165–72. Available from: doi:https://doi.org/10.1007/s00784-016-2004-z.

[39] Hadaya D, Soundia A, Freymiller E, Grogan T, Elashoff D, Tetradis S, et al. Nonsurgical management of medication-related osteonecrosis of the jaws using local wound care. J Oral Maxillofac Surg [Internet]. 2018 Nov;76(11):2332–9. Available from: doi:https://doi.org/10.1016/j.joms.2018.05.025.

[40] Valente NA, Chatelain S, Alfonsi F, Mortellaro C, Barone A. Medication-related osteonecrosis of the jaw: the use of leukocyte-platelet-rich fibrin as an adjunct in the treatment. J Craniofac Surg [Internet]. 2019 Jun;30(4):1095–101. Available from: doi:https://doi.org/10.1097/scs.0000000000005475.

[41] Tartaroti NC, Marques MM, Naclério-Homem M da G, Migliorati CA, Zindel Deboni MC. Antimicrobial photodynamic and photobiomodulation adjuvant therapies for prevention and treatment of medication-related osteonecrosis of the jaws: case series and long-term follow-up. Photodiagnosis Photodyn Ther [Internet]. 2020 Mar;29(December 2019):101651. Available from: doi:https://doi.org/10.1016/j.pdpdt.2020.101651.

[42] Vescovi P, Merigo E, Manfredi M, Meleti M, Fornaini C, Bonanini M, et al. Nd:YAG laser biostimulation in the treatment of bisphosphonate-associated osteonecrosis of the jaw: clinical experience in 28 cases. Photomed Laser Surg [Internet]. 2008;26(1):37–46. Available from: doi:https://doi.org/10.1089/pho.2007.2181.

[43] Vescovi P, Manfredi M, Merigo E, Meleti M, Fornaini C, Rocca J-P, et al. Surgical approach with Er:YAG laser on osteonecrosis of the jaws (ONJ) in patients under bisphosphonate therapy (BPT). Lasers Med Sci [Internet]. 2010 Jan;25(1):101–13. Available from: doi:https://doi.org/10.1007/s10103-009-0687-y.

[44] Sweeny L, Lancaster WP, Dean NR, Magnuson JS, Carroll WR, Louis PJ, et al. Use of recombinant bone morphogenetic protein 2 in free flap reconstruction for osteonecrosis of the mandible. J Oral Maxillofac Surg [Internet]. 2012 Aug;70(8):1991–6. Available from: doi:https://doi.org/10.1016/j.joms.2011.08.037.

[45] Andriani A, Petrucci MT, Caravita T, Montanaro M, Villivà N, Levi A, et al. Evolution of bisphosphonate-related osteonecrosis of the jaw in patients with multiple myeloma and Waldenstrom's macroglobulinemia: a retrospective multicentric study. Blood Cancer J [Internet]. 2012 Mar 23;2(3):e62. Available from: doi:https://doi.org/10.1038/bcj.2012.9.

[46] Vescovi P, Manfredi M, Merigo E, Guidotti R, Meleti M, Pedrazzi G, et al. Early surgical laser-assisted management of bisphosphonate-related osteonecrosis of the jaws (BRONJ): a retrospective analysis of 101 treated sites with long-term follow-up. Photomed Laser Surg [Internet]. 2012;30(1):5–13. Available from: doi:https://doi.org/10.1089/pho.2010.2955.

[47] Vescovi P, Merigo E, Meleti M, Manfredi M, Fornaini C, Nammour S. Surgical approach and laser applications in BRONJ osteoporotic and cancer patients. J Osteoporos [Internet]. 2012;2012:585434. Available from: doi:https://doi.org/10.1155/2012/585434.

[48] Franco S, Miccoli S, Limongelli L, Tempesta A, Favia G, Maiorano E, et al. New dimensional staging of bisphosphonate-related osteonecrosis of the jaw allowing a guided surgical treatment protocol: long-term follow-up of 266 lesions in neoplastic and osteoporotic patients from the university of bari. Int J Dent [Internet]. 2014;2014:935657. Available from: doi:https://doi.org/10.1155/2014/935657.
[49] Vescovi P, Giovannacci I, Merigo E, Meleti M, Manfredi M, Fornaini C, et al. 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 [Internet]. 2015 May;26(3):696–9. Available from: doi:https://doi.org/10.1097/SCS.0000000000001665.
[50] Vescovi P, Merigo E, Meleti M, Manfredi M, Guidotti R, Nammour S. Bisphosphonates-related osteonecrosis of the jaws: a concise review of the literature and a report of a single-centre experience with 151 patients. J Oral Pathol Med [Internet]. 2012 Mar;41(3):214–21. Available from: doi:https://doi.org/10.1111/j.1600-0714.2011.01091.x.
[51] Favia G, Tempesta A, Limongelli L, Crincoli V, Maiorano E. Medication-related osteonecrosis of the jaw: surgical or non-surgical treatment? Oral Dis [Internet]. 2018 Mar;24(1–2):238–42. Available from: doi:https://doi.org/10.1111/odi.12764.
[52] Romeo U, Galanakis A, Marias C, Vecchio A Del, Tenore G, Palaia G, et al. Observation of pain control in patients with bisphosphonate-induced osteonecrosis using low level laser therapy: preliminary results. Photomed Laser Surg [Internet]. 2011;29(7):447–52. Available from: doi:https://doi.org/10.1089/pho.2010.2835.
[53] V. Coviello, F. Peluso, S.Z. Dehkhargani, F. Verdugo, L. Raffaelli, P.F. Manicone, et al., Platelet-rich plasma improves wound healing in multiple myeloma bisphosphonate-associated osteonecrosis of the jaw patients, J Biol Regul Homeost Agents [Internet]. 26 (1) (2012) 151–155. Available from: https://www.cochranelibrary.com/central/doi/10.1002/central/CN-00842445/full.
[54] Longo F, Guida A, Aversa C, Pavone E, Di Costanzo G, Ramaglia L, et al. Platelet rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw: personal experience and review of the literature. Int J Dent [Internet]. 2014;2014:298945. Available from: doi:https://doi.org/10.1155/2014/298945.
[55] Bocanegra-Perez S, Vicente-Barrero M, Knezevic M, Castellano-Navarro JM, Rodriguez-Bocanegra E, Rodriguez-Millares J, et al. Use of platelet-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw. Int J Oral Maxillofac Surg [Internet]. 2012 Nov;41(11):1410–5. Available from: doi:https://doi.org/10.1016/j.ijom.2012.04.020.
[56] O. Dincă, S. Zurac, F. Stăniceanu, M.B. Bucur, D.C. Bodnar, C. Vlădan, et al., Clinical and histopathological studies using fibrin-rich plasma in the treatment of bisphosphonate-related osteonecrosis of the jaw, Romanian J. Morphol. Embryol. 55 (3) (2014) 961–964.
[57] Nørholt SE, Hartlev J. Surgical treatment of osteonecrosis of the jaw with the use of platelet-rich fibrin: a prospective study of 15 patients. Int J Oral Maxillofac Surg [Internet]. 2016 Oct;45(10):1256–60. Available from: doi:https://doi.org/10.1016/j.ijom.2016.04.010.
[58] Mauceri R, Panzarella V, Maniscalco L, Bedogni A, Licata ME, Albanese A, et al. Conservative surgical treatment of bisphosphonate-related osteonecrosis of the jaw with Er,Cr:YSGG laser and platelet-rich plasma: a longitudinal study. Biomed Res Int [Internet]. 2018;2018:3982540. Available from: doi:https://doi.org/10.1155/2018/3982540.
[59] Petrucci MT, Gallucci C, Agrillo A, Mustazza MC, Foà R. Role of ozone therapy in the treatment of osteonecrosis of the jaws in multiple myeloma patients. Haematologica [Internet]. 2007;92(9):1289–90. Available from: doi:https://doi.org/10.3324/haematol.11096.
[60] A. Agrillo, F. Filiaci, V. Ramieri, E. Riccardi, D. Quarato, C. Rinna, et al., Bisphosphonate-related osteonecrosis of the jaw (BRONJ): 5 year experience in the treatment of 131 cases with ozone therapy, Eur. Rev. Med. Pharmacol. Sci. 16 (12) (2012 Nov) 1741–1747.
[61] Pautke C, Bauer F, Otto S, Tischer T, Steiner T, Weitz J, et al. Fluorescence-guided bone resection in bisphosphonate-related osteonecrosis of the jaws: first clinical results of a prospective pilot study. J Oral Maxillofac Surg [Internet]. 2011;69(1):84–91. Available from: doi:https://doi.org/10.1016/j.joms.2010.07.014.
[62] Otto S, Ristow O, Pache C, Troeltzsch M, Fliefel R, Ehrenfeld M, et al. Fluorescence-guided surgery for the treatment of medication-related osteonecrosis of the jaw: a prospective cohort study. J Cranio-Maxillofacial Surg [Internet]. 2016;44(8):1073–80. Available from: doi:https://doi.org/10.1016/j.jcms.2016.05.018.
[63] Pelaz A, Junquera L, Gallego L, Garcia-Consuegra L, Junquera S, Gomez C. Alternative treatments for oral bisphosphonate-related osteonecrosis of the jaws: a pilot study comparing fibrin rich in growth factors and teriparatide. Med Oral Patol Oral Cir Bucal [Internet]. 2014 Jul;19(4):e320-6. Available from: doi:https://doi.org/10.4317/medoral.19458.
[64] Kim KM, Park W, Oh SY, Kim H-J, Nam W, Lim S-K, et al. Distinctive role of 6-month teriparatide treatment on intractable bisphosphonate-related osteonecrosis of the jaw. Osteoporos Int [Internet]. 2014 May;25(5):1625–32. Available from: doi:https://doi.org/10.1007/s00198-014-2622-8.
[65] Scoletta M, Arduino PG, Reggio L, Dalmasso P, Mozzati M. Effect of low-level laser irradiation on bisphosphonate-induced osteonecrosis of the jaws: preliminary results of a prospective study. Photomed Laser Surg [Internet]. 2010;28(2):179–84. Available from: doi:https://doi.org/10.1089/pho.2009.2501.
[66] Kim J-W, Kim S-J, Kim M-R. Leucocyte-rich and platelet-rich fibrin for the treatment of bisphosphonate-related osteonecrosis of the jaw: a prospective feasibility study. Br J Oral Maxillofac Surg [Internet]. 2014 Nov;52(9):854–9. Available from: doi:https://doi.org/10.1016/j.bjoms.2014.07.256.
[67] Szentpeteri S, Schmidt L, Restar L, Csaki G, Szabo G, Vaszilko M. The effect of platelet-rich fibrin membrane in surgical therapy of medication-related osteonecrosis of the jaw. J Oral Maxillofac Surg [Internet]. 2020 Dec; Available from: doi:https://doi.org/10.1016/j.joms.2019.12.008.
[68] Freiberger JJ, Padilla-Burgos R, Chhoeu AH, Kraft KH, Boneta O, Moon RE, et al. Hyperbaric oxygen treatment and bisphosphonate-induced osteonecrosis of the jaw: a case series. J oral Maxillofac Surg [Internet]. 2007 Jul;65(7):1321–7. Available from: doi:https://doi.org/10.1016/j.joms.2007.03.019.
[69] Atalay B, Yalcin S, Emes Y, Aktas I, Aybar B, Issever H, et al. Bisphosphonate-related osteonecrosis: laser-assisted surgical treatment or conventional surgery? Lasers Med Sci [Internet]. 2011 Nov;26(6):815–23. Available from: doi:https://doi.org/10.1007/s10103-011-0974-2.
[70] Angiero F, Sannino C, Borloni R, Crippa R, Benedicenti S, Romanos GE. Osteonecrosis of the jaws caused by bisphosphonates: evaluation of a new therapeutic approach using the Er:YAG laser. Lasers Med Sci [Internet]. 2009 Nov;24(6):849–56. Available from: doi:https://doi.org/10.1007/s10103-009-0654-7.
[71] Marx RE, Carlson ER, Eichstaedt RM, Schimmele SR, Strauss JE, Georgeff KR. Platelet-rich plasma: growth factor enhancement for bone grafts. Oral Surg Oral Med Oral Pathol Oral Radiol Endod [Internet]. 1998;85(6):638–46. Available from: doi:https://doi.org/10.1016/s1079-2104(98)90029-4.
[72] Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. J Am Med Assoc [Internet]. 2000;283(15):2008–12. Available from: doi:https://doi.org/10.1007/978-94-007-3024-3_10.
[73] Adornato MC, Morcos I, Rozanski J. The treatment of bisphosphonateassociated osteonecrosis of the jaws with bone resection and autologous platelet-derived growth factors. J Am Dent Assoc [Internet]. 2007;138(7):971–7. Available from: doi:10.14219/jada.archive.2007.0294.
[74] Choukroun J, Diss A, Simonpieri A, Girard M-O, Schoeffler C, Dohan SL, et al. Platelet-rich fibrin (PRF): a second-generation platelet concentrate. Part IV: clinical effects on tissue healing. Oral Surg Oral Med Oral Pathol Oral Radiol Endod [Internet]. 2006;101(3):e56–60. Available from: doi:https://doi.org/10.1016/j.tripleo.2005.07.011.
[75] Ramaglia L, Guida A, Iorio-Siciliano V, Cuozzo A, Blasi A, Sculean A. Stage-specific therapeutic strategies of medication-related osteonecrosis of the jaws: a systematic review and meta-analysis of the drug suspension protocol. Clin Oral Investig [Internet]. 2018;22(2):597–615. Available from: doi:https://doi.org/10.1007/s00784-017-2325-6.
[76] Chen D, Zhao M, Mundy GR. Bone morphogenetic proteins. Growth Factors [Internet]. 2004;22(4):233–41. Available from: doi:https://doi.org/10.1007/978-1-4471-5451-8_118.
[77] Cano-Durán JA, Peña-Cardelles JF, Ortega-Concepción D, Paredes-Rodríguez VM, García-Riart M, López-Quiles J. The role of Leucocyte-rich and platelet-rich fibrin (L-PRF) in the treatment of the medication-related osteonecrosis of the jaws (MRONJ). J Clin Exp Dent [Internet]. 2017;9(8):e1051–9. Available from: doi:https://doi.org/10.4317/jced.54154.
[78] Epstein MS, Wicknick FW, Epstein JB, Berenson JR, Gorsky M. Management of bisphosphonate-associated osteonecrosis: pentoxifylline and tocopherol in addition to antimicrobial therapy. An initial case series. Oral Surg Oral Med Oral Pathol Oral Radiol Endod [Internet]. 2010;110(5):593–6. Available from: doi:https://doi.org/10.1016/j.tripleo.2010.05.067.
[79] Koneski F, Popovic-Monevska D, Gjorgoski I, Krajoska J, Popovska M, Muratovska I, et al. In vivo effects of geranylgeraniol on the development of bisphosphonate-related osteonecrosis of the jaws. J Cranio-Maxillofacial Surg [Internet]. 2018 Feb;46(2):230–6. Available from: doi:https://doi.org/10.1016/j.jcms.2017.11.007.
[80] Cicciù M, Herford AS, Juodžbalys G, Stoffella E. Recombinant human bone morphogenetic protein type 2 application for a possible treatment of bisphosphonates-related osteonecrosis of the jaw. J Craniofac Surg [Internet]. 2012 May;23(3):784–8. Available from: doi:https://doi.org/10.1097/SCS.0b013e31824dbdd4.
[81] Cella L, Oppici A, Arbasi M, Moretto M, Piepoli M, Vallisa D, et al. Autologous bone marrow stem cell intralesional transplantation repairing bisphosphonate related osteonecrosis of the jaw. Head Face Med [Internet]. 2011 Aug;7:16. Available from: doi:https://doi.org/10.1186/1746-160X-7-16.
[82] Gonen ZB, Bilge S, Onder ME, Etoz O, Bahar D, Alkan A. Preventive effect of dental pulp-derived mesenchymal stem cells in experimental medication-related osteonecrosis of the jaw. Int J Oral Maxillofac Surg [Internet]. 2017;46:143. Available from: doi:https://doi.org/10.1016/j.ijom.2017.02.494.
[83] Ragazzo M, Trojan D, Spagnol L, Paolin A, Guarda Nardini L. Use of amniotic membrane in the treatment of patients with BRONJ: two case reports. J Surg case reports [Internet]. 2018 Apr;2018(4):rjy073. Available from: doi:https://doi.org/10.1093/jscr/rjy073.