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Literature Review Article

Antimicrobial photodynamic therapy in the treatment of medication-related osteonecrosis of the jaw: a scoping review

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Abstract

Introduction: There is a lack of consensus regarding management of medication-related osteonecrosis of the jaws (MRONJ). Antimicrobial photodynamic therapy (aPDT) may be a promising treatment. **Objective:** To broadly review the literature on the use of aPDT in MRONJ prevention or treatment. **Material and methods:** Medline-PubMed, Web of Science, Scopus, and Cochrane Library databases were reviewed for articles up to February 2023. From a total of 2084 studies, two were selected. **Results:** MRONJ was most frequently diagnosed in females with an average age of 60 years. Alendronate was the most reported causal bisphosphonate, and osteoporosis was the most common underlying disease. aPDT was performed with 0.01% methylene blue and its derivative, 0.01% phenothiazine chloride. aPDT was effective both in prevention and treatment of MRONJ. However, its use has always been associated with antibiotic therapy before and/or after treatment. **Conclusion:** There is insufficient evidence of the efficacy of isolated use of aPDT in MRONJ treatment and/or prevention.

Introduction

Medication-related osteonecrosis of the jaws (MRONJ) is an important adverse effect of bone-modifying drugs [30]. Among the drugs related to this disease, bisphosphonates and RANKL inhibitors, such as denosumab, are the most frequently reported [5, 22]. Patients undergoing chemotherapy for bone metastasis are at most risk, but osteoporosis treatment is also a risk factor [1]. This condition is characterized by the presence of avascular exposed necrotic bone, of eight or more weeks duration, in individuals in current treatment with bone-modifying agents or a history of their use, with no records of radiotherapy or metastasis in the jaw [30].

To date, there is no established treatment for this condition, which can significantly impair quality of life [9]. Several strategies have been proposed, including surgical debridement, which can be challenging due to an intrinsically difficult bone repair [23]. Therefore, conservative strategies for MRONJ management have been encouraged in early stages of disease, and as adjuvant to surgical approaches.

The pathogenesis of this disease is not completely understood, but there is some agreement that dental procedures, such as extractions, may increase the risk of its occurrence [16]. A link between its occurrence and dental infections implies a role for microbiota [11]. This is supported by the partial effectiveness of antibiotics, mostly in earlier stages of the disease [35]. This has led to the exploration of its use as a preventive approach with drug administration during dental procedures. However, data reported in the literature conflict [4, 6].

For this reason, antimicrobial photodynamic therapy (aPDT) may be a viable alternative. This modality consists of the use of a non-toxic photosensitizing dye with a light source emitting an appropriate wavelength, resulting in the production of reactive oxygen species (ROS), especially singlet oxygen ($^1O_2$) [13]. An oxidative environment leads to a selective destruction of microorganisms and damage to plasma membrane and DNA pathogen's. Recently, aPDT has been incorporated in several dentistry specialties, as an ally in decontamination of caries, root canals, periodontal treatment, and wounds [8, 20, 21]. The lack of toxicity and microbial resistance, compared with systemic antibiotics, are among its benefits [26]. Moreover, its application can be safely reproduced and performed in an ambulatory setting, which allows its widespread use in prevention of MRONJ. Therefore, this study aims to summarize current evidence regarding aPDT application in the prevention and treatment of MRONJ.

Material and methods

Search strategy

A literature search was conducted using the databases Medline/PubMed, Web of Science, Scopus, and Cochrane, including studies up to February 2023. Medline/PubMed search strategy consisted of the following:

#1 – Osteonecrosis[Mesh Terms] OR Osteonecrosis[Title/abstract] OR Bone Necrosis[Title/abstract] OR ARONJ[Title/abstract] OR BRONJ[Title/abstract] OR ONJ[Title/abstract] OR MRONJ[Title/abstract] OR "osteonecrosis of the jaw"[Title/abstract] OR "bisphosphonate-related osteonecrosis of the jaw"[Title/abstract] OR "bisphosphonate-related ONJ"[Title/abstract] OR "bisphosphonate-associated osteonecrosis of the jaw"[Title/abstract] OR "medication-related osteonecrosis of the jaw" [Title/abstract].

#2 – Photochemotherapy [Mesh Terms] OR Photodynamic therapy[Title/abstract] OR Phototherapy[Mesh Terms] OR Low-Level Light Therapy[Mesh Terms] OR Laser Therapy[Mesh Terms] OR Laser[Title/abstract] OR Photobiomodulation[Title/abstract] OR Low-Power Laser Therapy [Title/abstract] OR Low-Level Laser Therapy[Title/abstract] OR Low-Power Laser Irradiation[Title/abstract] OR Laser Biostimulation[Title/abstract] OR Photosensitizing Agents[MeSH Terms] OR Photosensitizing Agents[Title/abstract] OR Photosensitizing Effect[Title/abstract] OR Methylene Blue[Mesh Terms] OR Methylene Blue[Title/abstract].

#3 = #1 AND #2

This search was adapted to Scopus, Web of Science, and Cochrane databases. In addition, a manual search was performed using the reference lists of selected studies.

All studies enrolling adults were eligible, including randomized and non-randomized clinical trials, retrospective and prospective cohorts, case-control, and case series. Studies were restricted to those with participants with a history of use of bisphosphonates or other bone modifiers plus dental extractions or other minor oral surgery.

To review the efficacy of aPDT for both preventive and therapeutic measures, studies that

used aPDT following dental extraction or a diagnosis of MRONJ were included. When applicable, the absence of aPDT treatment was considered as the control group. No other criterion was imposed, but literature reviews and *in vitro* and *in vivo* animal studies were excluded.

Both study selection and data extraction were performed independently by two researchers (ABGC and SMCL), and a third researcher resolved discrepancies (TBBC). The following variables were extracted: publication data (author, year of publication), number of patients enrolled, mean age, underlying disease, information about antiresorptive drug (drug, administration route, drug holiday). Specific data about aPDT parameters were also compiled: photosensitizer used, pre-irradiation time, laser type, wavelength, and dosimetry (power density and irradiation time).

If aPDT was used as a preventive measure, we extracted data about the procedure type and the site. With studies that applied aPDT for MRONJ treatment, we also extracted information about a possible trigger/related event, site of the lesion, MRONJ stage, and healing. Literature was synthesized in a narrative fashion.

Results

The electronic search retrieved 904 studies, of which 622 were screened for eligibility after removal of duplicates. Titles and abstracts were analyzed, and 19 studies were selected for full-text reading. Initially, only one case series study was included [32]. Subsequently, an additional case report was included after manual research [27]. The reasons for exclusion are reported in figure 1.

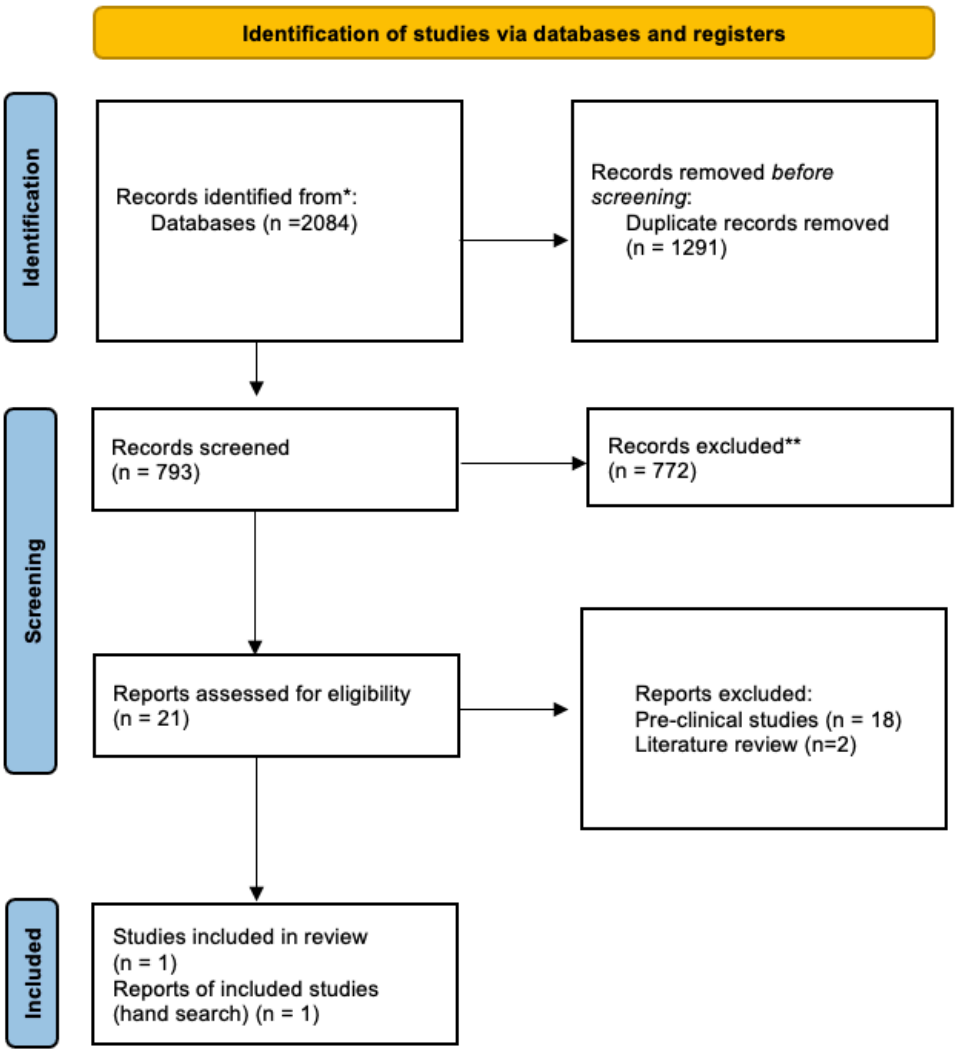

Figure 1 – Prisma flowchart of study selection in this review

aPDT in MRONJ prevention

Both studies addressed aPDT use in the prevention of MRONJ, as summarized in table I. The total sample size was 29 patients, predominantly female. Both studies included participants with a mean age of over 60 years. Poli *et al.* [27] reported clodronate (intramuscular route) and denosumab (subcutaneous) as the most frequently used antiresorptive agents. Additionally, this study reported that a drug holiday was adopted in four patients who had been using the drug for at least 3 years. Tartaroti *et al.* [32] reported that alendronate (oral route) was the most prescribed drug. This study also showed that a drug holiday was established in patients on zoledronic acid (intravenous) use for more than six months. For patients using alendronate, this procedure was adapted to those with more than ten years of therapy.

Both studies reported osteoporosis and breast cancer as the most frequent underlying diseases. Dental extractions on the mandibular jaw were the most frequent procedures. Both studies used methylene blue derivatives as photosensitizer and diode laser for tissue irradiation after pre-irradiation times as shown in table II.

Table I – Demographic characteristics from population of studies that addressed aPDT as preventive measure to MRONJ

Author/ year	Number of patients/ gender	Underlying disease	Age (±SD)	Drug/ administation route	Mean treatment duration (in months)	Drug holiday	Surgical procedure	Jaw
Poli *et al.* (2019) [27]	8 (female) 3 (male)	Osteoporosis (11)	72.5± 4.2	Clodronate – intramuscular (4) Alendronate – oral (3) Denosumab – subcutaneous (4)	39.2± 15.4	Yes (4) No (7)	Multiple extractions (9) Extraction + implants (2)	Mandible (5) Maxila (6)
Tartaroti *et al.* 2020 [32]	18 (female)	Osteoporosis (11) Osteopenia (2) Breast cancer (4) Other (1)	68.9± 11.7	Pamidronate – oral (1) Alendronate – oral (10) Risedronate – oral (2) Ibadronate – oral (1) Zoledronic acid – intravenous (4)	Minimum of 4	Yes (6) No (12)	Multiple extractions (18)	Mandible (10) Maxila (8)

Subtitle: SD – standard deviation

Table II – aPDT specifications in included studies

Author/year	Photosensitizer	Pre-irradiation time	Laser	Wavelength	Power density and irradiation time
Poli *et al.* (2019) [27]	Phenothyazine chloride 0.01% (methylene blue derivative)	3 minutes	Diode	660±10 nm	60 mW/cm^2 60 seconds
Tartaroti *et al.* (2020) [32]	Methylene blue 0.01%	5 minutes	Diode	660±10 nm	3.57mW/cm^2 90 seconds

Subtitle: mW – miliwatts; nm – nanometers

In the study by Tartaroti *et al.* [32], no patient undergoing preventive treatment with aPDT developed MRONJ after surgical procedures (dental extractions or minor oral surgery). Preventive treatment included the use of prophylactic antibiotic 24 hours before the surgical procedure, maintenance of good oral hygiene, and daily use of chlorhexidine solution 0.12%.

Efficacy of aPDT for the treatment of MRONJ: Tartaroti *et al.* study

Only Tartaroti *et al.* [32] addressed aPDT as a tool in the treatment of MRONJ (table III). The total sample was 15 participants, all females, with a mean age of 73.37±9.97 years. Nine of them had a history of dental extraction, three had experienced a local trauma, two presented at the dental implant site, and three had local periodontitis. The most frequent site of exposure was the mandible. Alendronate was the most prescribed drug among participants, and the most frequent clinical indications were osteoporosis or breast cancer.

Table III – Demographic characteristics from population of study that addressed aPDT as a treatment to MRONJ

Author/ year	Number of patients/ sex Mean age (±SD)	Underlying disease	Drug/ administration route	Mean treatment duration (months)	Drug holiday	Related previous event	Lesion site	MRONJ stage	MRONJ heal
Tartaroti et al. (2020) [32]	15 (female) 73.3± 9.97	Osteoporosis (11) Breast cancer (3) Osteopenia (2) prostate cancer/ Multiple myeloma (1)	Pamidronate – oral (1) Alendronate – oral (12) Risedronate – oral (1) Zoledronic Acid – intravenous (3)	Minimum 24 months	NR	Extractions (9) Periodontitis (3) Dental Implant (2) Trauma (3)	Mandible (12) Maxilla (5)	Stage 0 (1) Stage 1 (6) Stage 2 (8) Stage 3 (2)	Yes (16) No (1)

Subtitle: NR – not report

aPDT-related parameters were the same as those used for preventive use. Pre-irradiation time was 5 minutes, diode laser was used, and 660 ± 10 nm wavelength applied. A power density of 3.57mW/cm^2 was chosen, and the photosensilized tissue was irradiated for 90 seconds.

Preoperative aPDT ranged from 4 to 12 sessions, dependent on local inflammation and the patient's systemic condition; it was maintained until remission of symptoms. Photobiomodulation therapy was used for clinical benefit in 70% of cases. Most (88%) patients received prophylactic and postoperative antibiotics to minimize the risk of local and disseminated infection.

Discussion

Increases in life expectancy have led to a change in the profiles of patients seeking adjunct clinical care and an increase of interventions in patients using systemic medications. In this context, increased use of antiresorptives and antiangiogenics is associated with the occurrence of MRONJ, an important adverse effect that impacts the patient's quality of life [34]. Antiresorptive drugs are indicated for clinical situations in which there is a need for modulation of bone metabolism. They act on osteoclasts and their precursors, decreasing bone resorption. For this reason, they are used

in the treatment of osteolytic diseases, such as osteopenia and osteoporosis, and in adjuvant therapy regimens for bone metastases in cancer patients [2]. Antiresorptives can act on different bone resorption pathways. Bisphosphonates act mainly by adhering to the surface of the bone matrix and are endocytosed by osteoclasts when these cells take up bone [24, 25].

In addition, antiangiogenics, such as bevacizumab, may play a role in MRONJ. These drugs act to prevent vascular proliferation, which is efficient in combating some tumors, but can contribute to MRONJ occurrence as an adverse effect. Recently, other therapeutic drugs such as tyrosine kinase inhibitors, monoclonal antibodies, mammalian target rapamycin inhibitors, radiopharmaceuticals, selective estrogen receptor modulators, and immunosuppressants have been implicated in the pathogenesis of this disease, but their roles have not yet been fully elucidated [15].

According to Yarom *et al.* [34], drug therapy with antiresorptive and antiangiogenic drugs puts the individual at risk for developing MRONJ. Therefore, there is a need for a therapeutic approach in the management of this disease. Among the approaches described in the literature, some adjuvant treatments have shown promising results, including the potential of aPDT as a measure for the prevention and/or treatment of MRONJ. This treatment modality has shown promise in different clinical specialties, such as periodontics, endodontics, and surgery [3, 14, 33]. Despite that, there is little available evidence for the use of aPDT to prevent or treat MRONJ. The newness of this approach might explain the absence of randomized clinical trials in the present review.

The most frequently used antiresorptive drugs in the included studies were from the bisphosphonate class: alendronate (oral), in the study by Tartaroti *et al.* [32], and clodronate (intramuscular route) in the study by Poli *et al.* [27]. MRONJ has a higher prevalence in women, probably because of the use of bisphosphonates for the treatment of diseases such as osteoporosis and breast cancer [30]. Patients receiving bisphosphonate therapy need special oral health care, reinforcing the value of communication between physicians and dentists [17].

Antiresorptive and antiangiogenic drugs are usually prescribed in chronic diseases, which predominantly affect older patients. The present study found that patients, in both case series, had a mean age above 60 years. The use of antiangiogenics was not reported among the included studies, indicating a need to investigate the incidence of MRONJ in these patients, as well as research into aPDT for its prevention and treatment [31].

Poli's study reported a drug holiday for four patients when the duration of drug therapy was longer than 3 years [27]. In the Tartaroti *et al.* study, a drug holiday occurred in patients with intravenous therapy with zoledronic acid for longer than 6 months, and in patients who used oral alendronate for more than 10 years [32]. This regimen is controversial in the literature, as it does not provide clear evidence of benefits in many cases. For instance, an expert panel of cancer specialists stated that evidence neither supports nor refutes this practice [34].

Most patients in the present review reported a history of tooth extractions where the most frequent site of exposure was the mandible. Surgical manipulation is described as one of the main risk factors for the development of MRONJ [10, 12]. The first published study describing the occurrence of MRONJ reported a high proportion of cases in the mandible [18]. Several factors, such as a dense cortex and low vascularization, may explain this phenomenon. The risk of medication-related osteonecrosis of the jaws is heightened, in comparison to other bones, by the continuous trauma and direct exposure to the environment [19].

Comorbidities have also been reported in the pathogenesis of MRONJ. According to Otto *et al.* [24], smokers and patients with anemia, diabetes, or some other conditions are more likely to develop MRONJ and are at a higher risk of severity once it occurs [24, 29].

aPDT consists of the administration of a photosensitizer that, after low-level laser irradiation, generates substrates cytotoxic for microorganisms, with efficacy reported in the *in vitro* and *in vivo* literature against bacteria, viruses, and fungi, including drug-resistant strains [7]. One reason for the administration of aPDT in MRONJ is the presence of pathogens associated with these lesions, such as gram-positive bacteria [30]. Since its initial description, aPDT has been used with various substances and equipment: methylene blue derivatives, photosensitizers, stimulation by diode laser, and varied energy density and irradiation time.

aPDT is a noninvasive procedure that is easy to apply, without bleeding or side effects [7, 28]. Due to its favorable safety profile, the results presented in the two selected studies show that aPDT may be an effective alternative in the prevention and management of MRONJ.

These studies present aPDT as an adjuvant therapy in the prevention and treatment of MRONJ.

Several approaches are described, including the use of antibiotic therapy before and after any surgical procedure, such as tooth extractions, combined with aPDT. In addition, oral hygiene strategies and the use of topical mouthwashes have been used in prevention and treatment protocols for MRONJ. As it is a multifactorial complication, its treatment sometimes requires different approaches, as demonstrated in different protocols in the literature [30, 34].

The included studies have methodological limitations, such as the lack of clarity regarding the operator of surgical procedures, and the impossibility of isolating the effects of aPDT from the effects of mouthwashes and antibiotics. A larger sample and the inclusion of a control group without laser treatment could clarify the value of photonics in the prevention of MRONJ. In addition, various studies using laser light differ in protocols and parameters used by different authors. Therefore, randomized controlled studies are needed to define the real efficacy of aPDT in the prevention and treatment of MRONJ. However, it can be hypothesized that this therapy may have a promising role in both the prevention and treatment of MRONJ.

Conclusion

There is insufficient evidence regarding aPDT use in the prevention and treatment of MRONJ. Thus, despite its promising results, more studies are warranted to elucidate the real benefits of this therapy.

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