

## New trends in adjunctive treatment and diagnosis in Medication-related osteonecrosis of the jaw: A 10-year review

D. De Santis, F. Gelpi, U. Luciano, M. Zarantonello, A. Poscolere, N. Modena, P. Faccioni, G. Causarano, M. Finotti, F. Zotti, M. Magi, A. Iurlaro, P.F. Nocini, C. Alberti, A. Zangani, G. Capocasale, D. Donadello, R. Nocini and F. Bernardello

**Medication-related osteonecrosis of the jaw (MRONJ) is a major disease under study for over the last twenty years. Different classifications have been proposed and many therapies for the different stages have been applied. The evolution of treatments lead to an increasingly conservative approach. Numerous adjuvant treatments have been proposed in the last decade. All these complementary treatments have been proposed mainly to resolve or reduce the painful stress, predominantly caused by bacterial infection, simplifying the wound healing process and improving patients' compliance. Nowadays "secondary" treatments, such as autologous platelet concentrates (APCs, more specifically PRP, PRGF or PRF), hyperbaric oxygen (HBO), Auto/tetracycline fluorescence-guided bone surgery (AF-GBS/TF-GBS), medical drugs like teriparatide or the combination between pentoxifylline and tocopherol, fluorodeoxyglucose positron emission tomography (FDG-PET), laser and/or low-laser therapy and ozone therapy are more or less well documented and known considering their clinical effectiveness. The aim of the present review is the evaluation of the quantity and quality of scientific studies concerning this specific topic.**

At the beginning of 19th century first scientific publications appeared concerning serious pathologies, named "possy jaw", involving the upper and lower maxillary bone structures in specialized workers in the extraction and/or processing phosphorus (miners and workers in factories used to manufacture matches) (1). Originally noted as early as 2002 (2) the condition was first described in detail in 2003 when Marx et al. (3) published the first paper in which this pathology became known internationally and will be called Osteonecrosis of the Jaw (ONJ). A few years later it highlighted a very high incidence of this pathology (compared to the healthy population) in patients treated for various needs (e.g. osteoporosis, Paget disease, bone metastases, osteopetrosis, multiple myeloma) with bisphosphonates or undergo to radiation therapy. This correlation led scientific community to coin respectively the term Bisphosphonate-Related Osteonecrosis of the Jaws (BRONJ) and Osteo Radionecrosis of the Jaw (ORNJ). Furthermore, recent studies showed as other drugs categories (monoclonal antibody with anti-resorptive activity, anti-angiogenetic drugs (anti-VEGF), tirosin-Kinasi inhibitors, mTOR inhibitors) can cause the same disease, leading to a modification of the previous acronym in Medication-Related Osteonecrosis of the Jaws (MRONJ) by the American Association of Oral and Maxillofacial Surgeons (AAOMS) (4-5).

The MRONJ refers to a condition characterized by exposure of bone in the mandible or maxilla persisting for more than 8 weeks in a patient treated or in treatment with bisphosphonates with negative history of radiation therapy to the jaws (3-6). Diagnostic criteria for MRONJ were developed based on the pharmacological history as well as clinical and radiographic features (7). The MRONJ staging system, developed in 2006 by Ruggiero et al. and subsequently update in 2104 by AAOMS (4-5), is reported in Table I.

The classification in a specific stage cannot ignore an extreme accurate intra and extra oral clinical examination and an evaluation with radiographic supports (8); orthopantomography is the first level radiographic diagnostic support, followed by Computerized Tomography (CT) and Cone-Beam CT (CBCT); to obtain high-quality tomographic images, that exhibits a higher resolution in the alveolar bone and the jawbones (9); Magnetic Resonance Imaging (MRI) can be very useful (10-11). Recently the single-photon emission computed tomography (SPECT) has been used for localization of physiological changes in the bone and it appears to be sensitive but not specific (11).

In the assessment of osteoporosis' severity (and consequently the dosage, type and method of administration of the BPs), a quantitative haematic evaluation of two protein markers was introduced: P1NP (procollagen type 1 amino-terminal propeptide) and CTX (cross-linked C-telopeptide of type I collagen). These two parameters are measured before the start of therapy at time 0 and at 3 months, allowing to promptly verify the validity of the therapy and adherence to the treatment (12-13). Other widely used means in index calibration of osteoporosis and osteopenia's therapy with BPs are DEXA scan (dual energy x-ray absorptiometry) which yields to BMD (bone mineral density) values (14-16).

Although there are still no clear guidelines or a unique clinical protocol totally shared by the international scientific community, some operative strategies in osteonecrosis' case are worldwide shared by numerous clinicians. Summarizing in literature are reported: preferred conservative, endodontic maintenance therapies and extreme care of professional and home oral hygiene, avoiding traumatic interventions such as toilet or surgical curettage if possible, less extensive surgeries as possible, avoiding any traumatization for the

surrounding structures, intra-operative disinfection with saline solution, accurate management of soft tissues without stress or tension, elimination of sharp edges, closure by first intention with eventual flap passivation, double-layer suture, use of mouthwash and painkillers after surgeries, coverage or double antibiotic coverage variable from 10 days

before to 7 days after, weekly follow up. In absence of anamnestic allergy, the first-choice antibiotics are clavulanate amoxicillin and metronidazole (4, 14, 17-23). Aim of the present literature review is the evaluation of the possible utility of adjunctive therapies in the treatment and diagnosis of MRONJ.

## MATERIALS AND METHODS

This review study followed the PRISMA statement guidelines (24) and was conducted to analyze all publications related to adjunctive treatments on MRONJ therapy. Focused questions: what are today's additional treatments in the therapy of MRONJ? How many and what types of studies have been conducted on these treatments in the past 10 years? In the light of these data, could a first assessment be made of how much they are known and used in clinical practice by the scientific community?

Information sources: an electronic research was performed through MEDLINE (PubMed) databases. In addition, in order to further increase the number of eligible articles and not to skip potentially relevant publications, an analysis of the reference list of the main literature reviews and studies performed on the topic of interest was carried out. Search strategy: the electronic search was conducted by three independent examiners to minimize reviewer biases, applying the following filters: human studies, date of publication starting 01/01/2010 up to the time of the search (April 2020), and articles exclusively published in English. The first search strategy made use of the following terms: "adjunctive treatment MRONJ" or "adjunctive therapy MRONJ" or "adjunctive treatment ONJ" or "adjunctive therapy ONJ" or "adjunctive treatment BRONJ" or "adjunctive therapy BRONJ".

The first screening directly made on PubMed identified 75 papers, 54 on humans, 53 written in English, 48 published from 1st January 2020, 24 removing the duplicates and by a cross-checking in the different categories (in order to eliminate further duplications) the final result was 20 eligible papers (see Table II).

After removing duplicate and checking their pertinence, the total of evaluable publications was 18 (25-42). All the papers were analyzed by reading the abstract or, if it was not clear or incomplete, the full text. Nine complementary/additional treatments to usual therapy in osteonecrosis of the jaws were identified (see Table III). The adjunctive treatments are:

- APCs (Autologous Platelet Concentrates or hemoderivates, i.e. PRP, PRGF or PRF).
- HBO (Hyperbaric Oxygen).
- AF-GBS/TF-GBS (Auto/Fluorescence-guided bone surgery; Tetracycline/Fluorescence-guided bone surgery).
- Antimicrobial photodynamic therapy.
- Teriparatide.
- FDG-PET (Fluorodeoxyglucose Positron Emission Tomography).
- Pentoxifylline/Tocopherol.
- Laser and/or low-laser therapy.
- Ozone (O<sub>3</sub>).

The second step in screening was performed by searching for all 9 correlation items, as previously searched, with the terms "treatment", "MRONJ", "ONJ" and "BRONJ" (Table IV). For a better research about the term "APCs" it has been further divided into 3 subgroups (PRF, PRP and PRGF) (Table V).

### Eligibility criteria

The following inclusion and exclusion criteria were applied to carry out the study selection. Inclusion criteria:

- All kind of publication: Randomized-controlled clinical trials (RCT), Clinical trials (CT); Review (R); Longitudinal study (LS); Retrospective study (RS); Pilot study (PS); Case series (CS) and Case report (CR).
- "in vivo" studies, on humans.
- Date of publications from 01.01.2010.
- Original language English.
- Close relevance to MRONJ therapy (this point was discussed by examiners and accepted only if all 3-examiner agreed).
- Exclusion criteria:
- "In vitro" studies.
- Animal studies.
- Retrospective studies, case reports, case series, and systematic reviews.
- Date of publication before 01.01.2010.
- All original language, not in English.

Study selection: titles deriving from the research previously highlighted have been reviewed (identification) by three examiners. In case of disagreement, the three reviewers discussed each case jointly, to get to a final decision concerning inclusion or exclusion. The potentially useful articles through the analysis of the title were only then selected for a deeper investigation by firstly reading the abstract. In the examination of abstract (screening), attention was paid to assess the compliance of the study with the inclusion criteria. The selected studies were downloaded in digital or paper

version and submitted to the reading of the full text (eligibility). With this procedure only articles that conformed to the aforementioned criteria were included (included).

The data extraction was performed filling in a table (see Table V) with complementary treatments' name, typology of the study (RCT, CT, R, LS, RS, PS, CS, CR), total number of publication, number of discarded publication (not closely inherent for the purpose of the current study), total useful number of publication. Quality assessment. The following parameters were adopted for the evaluation of risk of bias: random sequence generation and allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective reporting (reporting bias), and other possible reasons for bias. Once these articles have been selected, they were further checked according to the same inclusion and exclusion criteria motioned above.

## RESULTS

All results are summarized in Table VI and Fig. 3. First of all, in Fig. 1 the observation on how the number of articles concerning the 8 additional treatments under consideration in decreasing order are: laser therapy (twenty-three), teriparatide (twentytwo), APCs (twenty), hyperbaric oxygen therapy (thirteen), ozone therapy (twelve), use of pentoxifylline/tocopherol (five), AF-GBS/TF-GBS (four) and FDG-PET (three). This data has the function of understanding passively through publications number whether a treatment has been taken into general scientific community consideration in order of its potential effectiveness.

From this point of view, data can be split into 4 different groups: the first one includes just the laser therapy which is better known and used than other additional treatment in MRONJ. The second one is made of teriparatide and APCs, the third one, progressively less utilized and mentioned in literature, are hyperbaric oxygen and ozone therapy. The last one, the fourth, highlights less known and used procedures to the current state of art in complementary therapy of MRONJ such as pentoxifylline/tocopherol medical drugs, whereas AF-GBS/TF-GBS is used as an aid in the pre-intra surgical phase and FDG-PET in diagnostic phase. Studies such as reviews and case reports (respectively 29 and 18) are more numerous than clinical trials, case series, retrospective studies, longitudinal studies, randomized clinical trials and pilot studies (respectively 9, 9, 7, 4, 2, 2) (Fig. 2).

## DISCUSSION

Despite progress in the prevention of BRONJ, a specific widely accepted and utilized treatment protocol to manage MRONJ is still missing, as the literature shows (43-48). Summarizing, the MRONJ treatments are referable to surgical and non-surgical treatments (49-60). In the past, surgical treatments were reserved only for advanced stages of BRONJ, but since 2012, the Italian Society of Oral and Maxillofacial Surgery (SICMF) and the Italian Society of Oral Pathology and Medicine (SIPMO) recommended conservative surgery in lesions belonging to stages 1 and 2. In this regard, from our study we evidenced as, in recent years, an attempt to increasingly adopt a "conservative" approach has been made. Most of the analyzed studies introduced the use of therapy defined as "additional" in association with surgery.

Specifically, additional therapy is referred to as non-invasive treatments, such as cycles of local or systemic antibacterial therapy combined or not, to low level laser therapy, ozone therapy (O3), HBO (Hyperbaric Oxygen therapy), the use of APCs APCs (Autologous Platelet Concentrates, such as PRP, PRGF or PRF), AF-GBS/TF-GBS (Auto/ Fluorescence-guided bone surgery, Tetracycline/ Fluorescence-guided bone surgery), Teriparatide, FDG-PET (Fluorodeoxyglucose Positron Emission Tomography) and the administration of Pentoxifylline/Tocopherol. The present study evidence that the most cited additional treatment in the literature is represented by the laser therapy, followed by administration of Teriparatide. The reported clinical outcomes in BRONJ/ONJ/ MRONJ treatments with additional therapies have been shown promising if compared to conventional surgery alone. For example, Vescovi et al. highlighted as the use of laser devices in MRONJ surgery represents a valid therapeutic option and enables the minimally invasive treatment of the early stages of the disease (61). With limits of the eligible study number, the analysis showed how most of the authors pointed out how these additional therapies are not substitutes of existing procedures, but they might be considered as a fundamental pre and/or post-operative steps to improve clinical outcomes and patient's life quality. A wider number of further prospective and retrospective studies, with a larger patients' samples, are needed to confirm this statement to better define the clinical effect of adjunctive therapies in MRONJ.