Anti-resorptive medications and periodontitis: critical appraisal, clinical management and ONJ risk

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ABSTRACT

Purpose: This manuscript critically appraised the literature on, and analyzed the clinical scenario of, osteo-metabolic patients affected by periodontitis.

Methods: A brief narrative review of literature was performed. The link between periodontitis and osteoporosis, the impact of anti-resorptive (AR) medications on the treatment of periodontitis, and the risk of medication-related osteonecrosis of the jaws (MRONJ) in different clinical scenarios were discussed.

Results: Data suggest a bidirectional link between periodontitis and osteoporosis. Patients affected by osteoporosis showed higher risk of periodontitis and periodontitis-induced tissue destruction. Even though treatment with AR medications has been hypothesized to reduce inflammatory periodontal bone resorption, it may not be suggested as an adjunctive intervention in the treatment of periodontitis. Four clinical scenarios were identified: patients waiting for AR treatment, patients treated with bisphosphonates for less than three years, patients treated with bisphosphonates for more than three years, and patients treated with denosumab. The risk of osteonecrosis in each of these cases is described and practical clinical recommendations are provided. Briefly, both non-surgical and surgical treatment of periodontitis may be beneficial for these patients.

Conclusions: Periodontitis treatment may be safe and predictable in patients treated with AR medications, keeping the MRONJ risk very low over time.

KEYWORDS

Anti-resorptive medications, bisphosphonate, periodontitis, MRONJ.

Background

Dentistry's interest in anti-resorptive (AR) drugs exploded in 2003. Marx described a case series of patients with osteonecrosis of the jaw (ONJ) associated with pamidronate and zolendronate administration [1]. Over the two decades since, improvements have been made in terms of diagnosis, definition, risk factors, and clinical management of medication-related osteonecrosis of the jaw (MRONJ) in patients affected by neoplasms were made [2-4].

Even though osteoporotic patients treated with AR drugs have been considered to be at higher risk of MRONJ [2-5], the clinical scenario of patients undergoing AR treatment for osteoporosis and affected by periodontitis has been less investigated. Osteoporosis and periodontitis have been extensively investigated and data suggest an association between these two diseases.

In Italy more than five million people are affected by osteoporosis [6] and AR therapy is commonly used to treat these patients. Moderate-severe periodontitis, on the other hand, is the sixth most frequent chronic non-communicable disease [7] and may affect up to 40% of the Italian population. Untreated periodontitis can lead to tooth loss [8]. Tooth extraction is considered the main trigger of MRONJ onset [2,3].

The aim of this study was to critically appraise the relevant literature and analyze the clinical scenario of the osteo-metabolic patient also affected by periodontitis.

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Osteoporosis and periodontitis: mechanistic link and epidemiological association

Periodontitis is a chronic multifactorial inflammatory disease characterized by progressive destruction of the supporting tissue of the teeth [9]. Bacterial plaque (dental biofilm) is the causative factor, while diabetes, smoking, genetic predisposi-

tion, and obesity are risk factors/indicators contributing to disease progression [10].

The disease phenotype, tissue destruction, and number of teeth lost may differ among subjects. Periodontitis is classified into four stages (1 to 4) on the basis of its severity and the complexity of the treatment [11].

Briefly, a frank dysbiosis within the dental sulcus may be associated, in predisposed patients, with a huge inflammatory response mediated by osteo-immunology pathways. Th-17 lymphocytes play a pivotal role in stimulating the periodontal ligament cells and osteoblasts to express RANKL, which leads to RANK-RANKL-OPG pathway-mediated destruction of the periodontal tissue [12].

Within this context, a role for periodontal infection/inflammation in systemic health/disease can be hypothesized. In particular, a bidirectional association between osteoporosis and periodontitis may be suggested, on the basis of shared risk factors (vitamin D deficiency, smoking), oxidative stress, and inflammatory pathways [13].

A systematic review including 23 observational studies and more than two million patients reported that osteoporotic patients had a twofold greater (OR 1.96) risk of having periodontitis compared with healthy controls [14]. Additionally, higher periodontal tissue destruction due to periodontitis was reported in osteoporotic post-menopausal women compared with healthy ones [15]. These data suggest an association between osteoporosis and periodontitis.

The impact of anti-resorptive drugs on periodontitis

Anti-resorptive drugs (i.e., bisphosphonates and denosumab) reduce bone resorption by inhibiting osteoclast activity or by binding to RANKL. In the 1990s, animal models were used to test whether bisphosphonates may reduce periodontitis-induced tissue destruction. Risedronate was found to positively impact bone mineral density and the number of osteoclasts in a dose-dependent manner in osteoporotic male Wistar rats, thus reducing periodontal tissue resorption [16].

Nevertheless, human randomized controlled trials failed to demonstrate an additional clinical benefit of bisphosphonate administration in patients undergoing non-surgical treatment of periodontitis [17-20].

In this setting, the adjunctive use of AR medications (bisphosphonates, denosumab) to treat periodontitis may not be advocated. In fact, the impact of AR medication on periodontitis treatment remains unclear, and all the studies had short follow-up durations (6 to 12 months) and cannot assess the risk of MRONJ. Within this context anabolic drugs may represent an alternative treatment [21].

Periodontitis and the risk of MRONJ

Periodontists are commonly involved in treating patients undergoing AR treatment. A recent survey of a cohort of 451 dentists found that almost all the participants (98.4%) had treated patients also undergoing AR treatment [22].

These patients' risk of developing ONJ has been reported. The prevalence of ONJ is 0.02%–0.05% in osteoporotic patients under treatment with AR medications, and may be increased to 7.2% by the presence of comorbidities (e.g., diabetes) [2,22,23]. Neoplastic patients under treatment with AR drugs had higher risk of ONJ (8–9.8%) [2,24].

Dental extraction is the main risk factor for the onset of MRONJ, while gingival inflammation and periodontal infection may play a role in increasing the risk [2,3]. Since periodontitis is an inflammatory disease caused by infection in the dental sulcus, and represents the main cause of dental extraction, an increased risk of developing ONJ can be hypothesized in periodontitis patients undergoing AR treatment. This hypothesis is supported by a meta-analysis which demonstrated that patients with MRONJ were more likely to have periodontitis than healthy controls, with a RR of 2.75 [26].

Research in animal models showed that inducing periodontitis, by means of ligature around the teeth in the presence of zolendronate i.v. administration, may induce ONJ in the rat [27]. On the other hand, a study in a similar animal model found that treating the periodontitis may prevent ONJ [28]. In fact, periodontal treatment reduces systemic inflammation and, above all, tooth loss in the long term. The latter is, as mentioned, the main risk factor for MRONJ onset.

Within this context, there is insufficient evidence to clearly state the role of periodontitis in increasing the risk of MRONJ onset. Nevertheless, since periodontal treatment along with a strict supportive periodontal therapy reduces the risk of a tooth extraction, it should be strongly advised also in osteoporotic patients undergoing AR treatment.

Clinical management of periodontal patients undergoing antiresorptive treatment for osteoporosis.

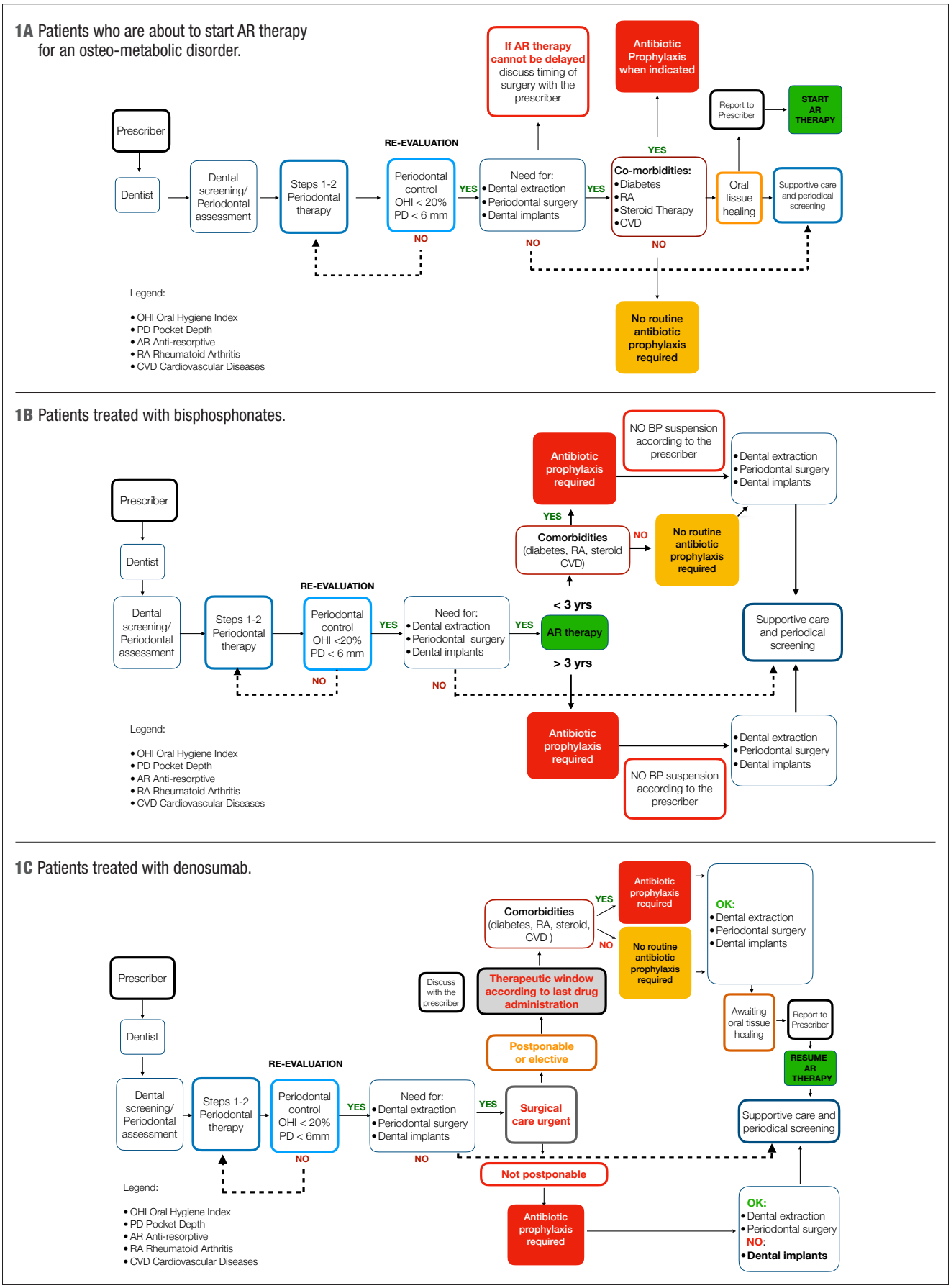
As mentioned, there has been less consideration, in the literature, of the clinical scenario of patients affected by periodontitis and undergoing AR treatment for osteoporosis. The incidence of MRONJ in these patients is very low, but considering the huge number of patients treated with AR drugs, the prevalence of periodontitis, and the impact of periodontal treatment on tooth loss, the clinical management of these patients may be crucial.

In addition, it should be considered that the risk of MRONJ increases with the years of AR administration, thus very long-term periodontal/dental monitoring of these patients may be advocated. In particular, different clinical case types may be identified, considering current evidence and AR administration (Fig.1, a-c) [29].

Patients waiting to undergo antiresorptive treatment for an osteo-metabolic disorder (Fig 1a)

It is highly advisable to educate patients about the long-term risk of MRONJ, which can be kept very low. In fact, they should be referred for a complete dental and periodontal examination before starting AR treatment. The dentist should

Figure 1 Clinical scenarios in the management of patients affected by periodontitis and in need of treatment or under treatment for osteoporosis (Adapted from [29]).



perform all necessary surgical procedures (dental extraction, periodontal surgery, implant therapy) before starting the AR treatment. The major aim is to remove all periodontal/dental infection and reduce the risk of tooth loss in the long term. In particular, non-surgical periodontal treatment is associated with infection and inflammation control and surgical periodontal treatment reduces the risk of tooth loss in the long term [30,31].Dental implants may also be performed. It is fundamental to enroll patients in a tailored supportive periodontal therapy program in order to ensure that the periodontium is kept stable over the very long term.

Patients taking bisphosphonates for an osteo-metabolic disorder for less than three years (Fig 1b)

These patients should have regular dental check-ups and be involved in a supportive periodontal therapy program. The risk of MRONJ can be kept very low.

In case of periodontitis, periodontal therapy steps I and II (i.e., non-surgical treatment) must be administered and if subsequent surgical periodontal treatment is indicated (step III), it may be carried out as well as dental implants. In particular, all the necessary surgical procedures may be performed after the periodontal infection control phase.

Antibiotic treatment should not be suggested routinely, although it may be considered in the event of comorbidities (i.e., diabetes, rheumatoid arthritis, corticosteroid treatment).

Patients taking bisphosphonates for an osteo-metabolic disorder for more than three years

Patients in this group are expected to be at increased risk of MRONJ, therefore optimal periodontal health and reduction of the need for dental extraction should be obtained before starting the AR treatment.

Nevertheless, this scenario is not a contraindication to perform the periodontal infection control phase (steps I and II), which must be carried out. If further dento/alveolar surgeries are needed (dental extraction, periodontal surgery), it is suggested to administer an antibiotic treatment. Unfortunately, considering the current evidence, there is no consensus on molecules or administration period. Both amoxicillin 1 g, TID and the combination of amoxicillin 1 g/metronidazole 500 mg, TID have been suggested. Surgeries must be performed under a strict periodontal control.

Considering the increased MRONJ risk, a long-term tailored supportive periodontal therapy program and periodic dental check-ups are mandatory.

Patients taking RANKL (denosumab) for an osteo-metabolic disorder (Fig 1c)

In this clinical scenario, too, optimal periodontal health and reduction of the need for dental extraction should be obtained before starting the AR treatment.

If periodontitis is present, the periodontal treatment steps I and II must be performed.

Dento/alveolar and periodontal surgeries may be delayed using a therapeutic window approach. In particular, considering the pharmacokinetics of denosumab, the best option appears to be to wait five months after the last administration, and subsequently to administer a new dose after a proper wound healing process (8 weeks). As suggested by some clinical recommendations [5], antibiotic prophylaxis may not be used routinely, although it may be administered in the event of comorbidities (i.e., diabetes, rheumatoid arthritis, corticosteroid treatment).

If dental surgeries (dental extraction) cannot be postponed, antibiotic treatment is mandatory.

Finally, close collaboration between prescribers and dentists/periodontists is of paramount importance. The best option for patients is clearly to reduce the need for further dental surgeries and/or dental extractions before starting AR treatment.

Nevertheless, dentists must not suggest that patients discontinue AR administration, and must closely interact with prescribers in order to establish the ideal timing of dental/periodontal treatments. This approach may increase the overall quality of the dental treatment for these patients, reducing their MRONJ risk in the long term.

Conclusion

Data from the literature point to an association between osteoporosis and periodontitis. Periodontitis treatment may be safe and predictable in patients treated with AR medications, keeping the MRONJ risk very low over time.

The clinical scenarios described in this manuscript may be useful both for prescribers and for dentists. Nevertheless, further studies are needed to investigate the potential impact and synergisms of AR prescription in these subjects and to improve the role of the multidisciplinary approach (endocrinologists, dentists, orthopedics, physiatrists).

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