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Original Article

Is medication related osteonecrosis of the jaw around implants a rare entity? A case series with a focus on etiopathophysiology

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ABSTRACT

Objectives: Medication Related Osteonecrosis of the Jaw (MRONJ) around dental implants is a rare complication of antiresorptive drug (ARD) treatment. MRONJ has been described in patients with implants placed before, during or after ARD treatment. The aim of this study was to review our cases and to discuss a preventive approach to avoid the risk of MRONJ around implants.
Materials and methods: In a retrospective analysis of the 168 MRONJ seen in our department from 2005 to 2021, we searched for cases of patients with MRONJ around dental implants.
Results: Six patients (4 females, 2 males) presented with MRONJ around 17 implants. Median age was 64 (50 −83) years. Four patients received ARD treatment for osteoporosis and 2 for cancer. The maxilla was more affected than the mandible. Six implants were placed after the initiation of ARD treatment and eleven were placed before initiation of ARD treatments. Eight implants were managed surgically while 9 implants were managed conservatively.
Conclusion: In this series, implants were placed before or after starting ARD treatment. Despite initial successful osseointegration, MRONJ occurred months or years after initiation of ARD treatment. The role of periimplantitis should be discussed as well as the role of microcracks in the bone following implant loading. Less is known over the effect of ARD treatment after implant osseointegration. Implants could be a risk factor for MRONJ and must be checked regularly (every 3 months). It is important to check the healthy and biomechanical harmony of the implant system during the pre-treatment assessment.

1. Introduction

Increased life expectancy in developed countries has boosted diseases affecting bone metabolism such as osteoporosis, and/or oncological diseases. At the same time, and despite improvements in dental health care, tooth loss is an increasing problem and the need for implant rehabilitation therapy is growing.

In the last 30 years, a new class of drugs known as Anti-Resorptive Drug (ARD) has been introduced whose first goal is to slow down bone turnover by targeting osteoclasts. Bisphosphonates (BP) and denosumab (DMab) are the most commonly used molecules.

ARDs are currently used for the treatment of osteoporosis and metabolic bone diseases, as well as metastatic skeletal malignancies and multiple myeloma [1,2].

Osteonecrosis of the jaw (ONJ) is the most common dreaded adverse event of ARD treatment and is associated with devastating side effects and high morbidity.

It was initially described by Marx [3] in association with BP therapy under the name Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ). Since then, multiple other molecules have been implicated such as DMab and antiangiogenic drugs (sunitinib, bevacizumab). This led to a change in the designation of the disease to Medication-Related Osteonecrosis of the Jaw (MRONJ) [4].

According to the American Association of Oral and MaxilloFacial Surgeons (AAOMFS), the definition of MRONJ is as follows: Current or previous treatment with antiresorptive or antiangiogenic agents; Exposed bone or fistula in the maxillofacial region that has persisted for longer than 8 weeks; No history of head and neck radiation or metastatic disease to the jaws [4].

The main known risk factors associated with MRONJ are oral surgery, infection, periodontal/periapical diseases, trauma and anatomic factor [5]. No cause was identified in 30% of cases. Other factors that may favour the occurrence of MRONJ are: route of administration (intravenous (IV) > subcutaneous (SC) > Oral), indication (bone metabolism / oncology), association with corticosteroid therapy, tobacco consumption, older age, systemic disease (diabetes, rheumatoid polyarthritis, anemia) [5–7].

Although still poorly understood, the pathophysiology of MRONJ seems to be multifactorial [8]. The main mechanisms involved are disruption of bone remodeling, inflammation or infection, impaired

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local immunity, soft tissue toxicity and inhibition of angiogenesis [8,9].

In 1995 Stark and Epker [10] described what appears to be the first case of osteonecrosis following implant surgery in the literature [10].

Little is known about the relation between implants and MRONJ. The literature on implants and ARD to date is ambiguous, heterogeneous, incomplete, and remains a controversial topic in the literature [11].

Although there is no consensus, the relative contraindications in the literature for implant placement in patients previously treated with ARD are more than 3 years of oral ARD, especially when associated with corticosteroid therapy, and the absolute contraindications are IV or SC administration regardless of the duration for oncological indication [4,12].

Despite the overall success rate of implants, implant could be a risk factor for MRONJ, either by its placement (ISTO: implant surgery-triggered osteonecrosis) but even more so by the presence of the implant itself into the bone and peri-implants disease (IPTO: implant presence triggered osteonecrosis) [13–16].

The aim of this study was to highlight risk factors for MRONJ around implants and define the type of MRONJ (IPTO or ISTO) in our series [16,17].

2. Material and methods

A retrospective study of all cases of MRONJ was conducted to identify cases of MRONJ around implants (Institutional review bord CEHF 2015/24SEP/511). The study was conducted between 03/2005 and 05/2021 and included patients referred and/or treated at the Cliniques Universitaires Saint-Luc (Brussels, Belgium).

Inclusion criteria were all patients with MRONJ around implants.

Exclusion criteria were incomplete files.

The diagnosis of MRONJ was made according to the criteria established by the AAOMS.

Each patient was allocated according to systemic, local and pharmacological factors and the treatment administrated. The following data were collected:

- Patient characteristics: o Sex o Age
  - Medical comorbidities: tobacco consumption, diabetes, hypertension, rheumatoid arthritis, anemia
  - Drug comorbidities: corticosteroids, chemotherapy, antihypertensive drugs.
  - ARD therapy indication: oncology, metabolic bone disease
- ARD characteristics: type, route of administration (IV, SC, Oral), timing and duration of ARD therapy
- Implant characteristics: location, environment, date of placement, presence of infection (periimplantitis)
- Oral status: radiological and clinical examination
- MRONJ characteristics: stage according to the AAOMS classification, bone exposure, suppuration, fistula
  - Treatment: medical, surgical
  - Evolution: stable disease, progression, healing, improvement

The conservative treatment protocol included local care (chlorhexidine and H2O2 mouthwash, daily dental plaque control), antibiotic therapy with amoxicillin/clavulanate 875/125 mg 2 to 3 times a day (depending on local signs of infection). In case of allergy, clindamycin 300 to 600mg 3 times a day was proposed. The follow-up was regular (minimum twice a month) until improvement of the symptoms or healing.

The surgical treatment included explantation, curettage, and/or sequestrectomy with or without Platelet rich fibrin placement.

The information has been included in an anonymized database (Excel 2016, MS office)

3. Results

3.1. Demography characteristic

MRONJ was present in 168 patients (67 osteoporotic patients and 101 oncology patients). Twelve patients present a total of 64 implants of which six patients presented with MRONJ around 17 implants.

In the osteoporotic group: 4/67 (5.97%) patients (14 implants) were affected by MRONJ around implants while 2/67 patients with 9 implants were affected by MRONJ at another site

In the oncology group: 2/101 (1.98%) patients (3 implants) were affected by MRONJ around implants, while 4 patients with 12 implants presented with MRONJ at another site

3.2. Patient characteristics (Table 1)

Six patients (4 women / 2 men) presented with MRONJ around implants, with an average age at the onset of the first symptom of 65.6 (50–83) years.

Table 1
Patient characteristics.

patient	Age	Indication ARD	comorbidities	ARD	Route of administration	ARD duration
1	78	OP	CS	Alendronate Zoledronate	oral iv	5 year
2	50	OP	HT CS	DMab	sc	3year
3	66	BC	IBP Palbociclib CKD	DMab	sc	3year
4	83	OP	HT CS Etanercept Tobacco Ankylosing spondylitis	Zoledronate	iv	3 year
5	55	OP	HT CS	Zoledronate	iv	2year
6	62	PC		DMab	sc	2year

OP osteoporosis ; BC breast cancer ; PC prostate cancer; HT hypertension; CKD chronic kidney disease; CS corticosteroids; iv: intraveinous; sc: subcutaneous.

3.3. Medical comorbidities

Patients comorbidities were high blood pressure (*n*=3), tobacco consumption (*n*=1), diabetes (*n*=1), stage III chronic renal failure (*n*=1) ankylosing spondylitis (*n*=1).

3.4. Drug comorbidities

Two patients were concomitantly treated with corticosteroids, 1 patient with Palbociclib (TKI), 1 patient with Etanercept (anti-TNFα).

3.5. ARD indication

Four patients were treated for bone metabolism disorder, 2 patients were treated for metastatic disease (1 prostate cancer and 1 breast cancer).

3.6. ARD characteristics

Three patients were treated with DMab (2 monthly, one 2 times a year), 2 patients with yearly zoledronic acid, 1 patient with alendronic acid with switch to yearly zoledronic acid.

Average duration of total ARD therapy was 3 (2–5) years before MRONJ.

3.7. Implant characteristics (Table 2)

The 6 patients presented with 43 implants out of which 17 (39.5%) were involved in the MRONJ process. Fifteen implants were placed posteriorly (9 maxillary and 6 mandibular) and 2 were located in the anterior maxilla.

Ten/24 quadrants were affected with 11 locations of MRONJ related to implants.

Of the 17 implants involved, 16 were in charge and only one not.

One patient presented with 3 foci of MRONJ related to implants, 3 patients with 2 foci, 2 patients with 1 focus.

Each focus involved 1.54 implants (1–4).

In the osteoporotic group, 14/35 (40%) implants were affected by MRONJ compared to 3/8 (37.5%) in the oncological group.

3.8. Chronologic characteristics (Fig. 1)

The series was divided into implants placed before ARD therapy and implants placed after ARD therapy.

Eleven implants were placed before ARD therapy with an average time of 8.27 (1–20) years between implant placement and initiation of ARD therapy.

In this group, the average time from ARD therapy to the onset of MRONJ was 4.27 (2–16) years. The average time from implant placement to the onset of MRONJ was 12.54 (5–22) years. Three patients were still treated by ARD at the moment of MRONJ.

Six implants were placed after ARD therapy with an average time of 6.3 (6 and 7) years after the start of ARD treatment (this case concerns the same patient). For this patient, the average time from ARD therapy to the onset of MRONJ is 11 (10–13) years, and the average time from implant placement to the onset of MRONJ is 4.6 (4–6) years.

All the implants presented with a good osseointegration before MRONJ. All the cases were IPTO.

3.9. MRONJ and management characteristics

Of the 11 foci of MRONJ, 9 were stage 2, and 2 were stage 3.

Eight implants were managed surgically while 9 implants were managed conservatively.

In total, of the 17 implants in the series, there were 14 explantations (7 spontaneous and 7 surgical).

Of the 6 patients, 1 patient had a MRONJ non-implant related.

One patient died due to oncological complication.

Of the 11 locations of MRONJ, 5 were stable and 6 healed.

4. Discussion

This series highlights the risk of MRONJ around implants in a small number of cases.

Implant therapy is based on the ability of an implant to osseointegrate. Osseointegration depends on a balanced bone metabolism throughout the implant's life under functional loading [18]. This bone metabolism could be disturbed by therapy with ARD [19].

This disruption of bone homeostasis has an ambivalent effect on the osseointegration of implants. On the one side, it allows an improvement of the primary stability but on the other side it considerably lengthens the achievement of the secondary stability (bone–to–implant contact (BIC) and bone area ratio (BA)). Nevertheless, in the end, the final stability of the implant seems to be improved [20–22].

Although still in the experimental stage, some authors suggest the use of BPs-coated implants to improve their osteointegration, arguing that the risk of osteonecrosis is low because the bone contamination

Table 2
implant characteristics.

patient	Implants/patient	Implant + MRONJ	Implant/foci	Time between implant placement and ARD (years)	Time between ARD and MRONJ (years)	MRONJ stage	treatment	treatment	evolution
1	15	7	4 Max P	-6	10	3	surgical	SuE	stable
			2 Max P	-7	13	2	medical	SpE	stable
			1 Max A	3	16	2	medical		stable
2	5	1	1 Mand P	8	3	3	medical		stable
3	7	1	1 Mand P	7	3	2	medical		stable
4	11	4	3 Mand P	20	2	2	surgical	SuE	healing
			1 Max P	3	6	2	medical	SpE	healing
5	2	2	1 Mand P	2	3	2	medical	SpE	healing
			1 Max A	1	4	2	medical	SpE	stable
6	3	2	1 Max P	5	3	2	surgical	SpE	healing
			1 Max P	2	3	2	medical	SpE	healing

Max P: maxilla posterior.
Max A: maxilla anterior.
Mand A: mandible anterior.
Mand P: mandible posterior.
SpE: spontaneous explantation.
SuE: surgical explantation.

of BPs is low (<1 mm). In case of infection, it would be easily managed by removing the contaminated bone layer [23,24].

Despite the slightly lower success of clinical osseointegration in patients under oral ARD therapy, implants could be a risk factor for developing MRONJ [25].

Two classes of implant failure are distinguished: early and late [26]. The early failure refers to implants that fail to osseointegrate, while the late failure refers to implant failures when osseointegration is established with functional implant loading.

While the early failure is most often concerned with biological complications (osseointegration defect), the late failure may concern biological (peri-implantitis) or mechanical (loading) complications [26].

Implant-related MRONJ are to be distinguished from classic implant failure as a singular type of implant failure. Usually, in case of implant failure, the implant is mobile and easy to remove without surrounding tissue, and the site normally heals after curettage [17].

In implant-related MRONJ, a distinction is made between MRONJ related to the insertion of the implant and MRONJ related to the presence of the implant itself. In the literature, they are distinguished from each other by a period that varies from 6 months to 1 year after the insertion of the implant. The first distinction between these two clinical entities was made by Lazarovici et al. [27] under the name of "implant presence-triggered osteonecrosis" (IPTO). To complete this distinction, the term "implant surgery triggered osteonecrosis" (ISTO) was brought by Kwon et al. [15].

It is interesting to note that most cases of MRONJ are IPTO related and few cases are ISTO related [16].

In our series, all the cases were IPTO related as the implants were previously osseointegrated for over a year.

As explained above, this lack of awareness makes implant-related MRONJ a difficult clinical entity to study. Because most of the prospective studies dealing with the subject are made over a short period of time, this constitutes a bias in the vision of this clinical entity in the literature.

In 2012, Kwon et al. [15] distinguished 3 histomorphological entities of implant-related MRONJ by deriving bone destruction type.

The *frozen type*: complete necrosis of the bone around the implant, which is similar to the classic implant failure except that it can occur years after the placement.

The *osteolytic type*: extensive osteolysis around the implant with or without sequestration (Fig. 2).

The *en block sequestration type*: bone sequestration with an implant maintaining direct bone osseointegration's contact with the implant (Figs. 3 and 4).

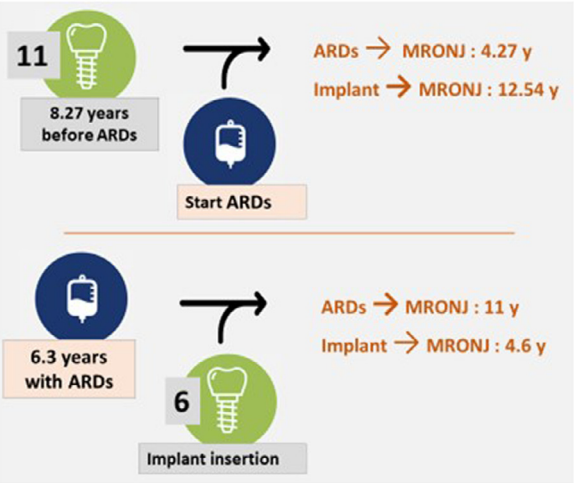

Fig. 1. Chronologic characteristics between implants, ARD therapy and MRONJ.

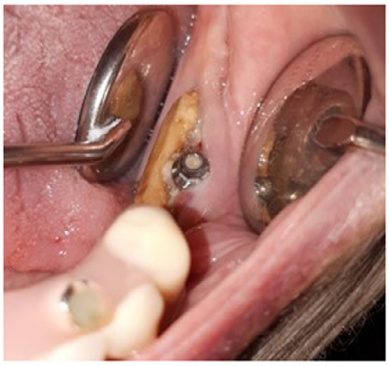

Fig. 2. MRONJ around implant 35, medical treatment, (osteolytic type).

In this case series, the *osteolytic type* (15 implants) and *en block sequestration type* (2 implants) were the most common types, probably because the frozen type often goes unnoticed and confused with a classical failure.

The pathophysiology of the implant-related MRONJ is even less well understood than that of MRONJ and also appears multifactorial. Nevertheless, the implant-related MRONJ seems to be related to the same risk factor (route of administration, ARD therapy indication, age, corticosteroid therapy, systemic disease...) which is consistent with our series. In two patients, other medication could be implicated in the MRONJ process: palbociclib (TKI) and etanercept (antiTNF-α).

Two mechanisms are frequently advanced in the occurrence of MRONJ related to implants. The inflammatory (or infectious) mechanism and the mechanical mechanism. These two mechanisms are not mutually exclusive and are probably linked to varying degrees, although the inflammatory mechanism appears to be the most predominant in the pathophysiology of implant-related MRONJ and is most frequently advanced by the authors.

The inflammatory mechanism is based on the importance of inflammatory processes in the etiology of MRONJ. Thus, several authors have elaborated a link with peri-implantitis and implant-related MRONJ [13,16, 28–30].

With this awareness, it could be inferred that the improvement of hygiene is essential to fight against MRONJ [31].

Most previous studies are retrospective and the data on these parameters were never measured or measured in a too heterogeneous way to be included.

To overcome this difficulty prospective studies are needed with the collection of parameters in a systematic and homogeneous way. This exposes to another difficulty, namely the realization of a study with a large number of individuals, because the implant-related

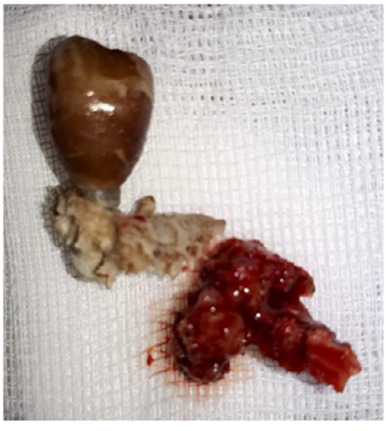

Fig. 3. Spontaneous explantation implant 16 and bone sequestration, additional sequestration curettage (en block sequestration type).

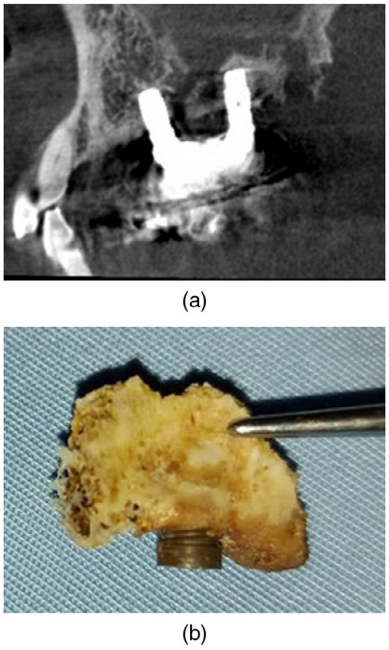

Fig. 4. a, b: same patient: MRONJ around implant 26, spontaneous explantation after removing the bridge (en block sequestration type).
Radiological and clinical aspect.

MRONJ frequency remains a rare event and moreover, over a long period because as seen above, most of the MRONJ related to implants develops after several years.

The second mechanism by which implant-related MRONJ could be induced is related to the change in mechanical properties of the bone. Indeed, ARD therapy has an impact not only on bone quantity, but also on bone quality. Thus, ARD increases the bone mass density (BMD) which is associated with a decreased risk of fracture (as shown by the FRAX's score), but also with an increase in mineralization and mechanical properties of the bone. These mechanical changes take place at a fundamental parameter and macro-micro-nano structural level and lead paradoxically to a deterioration of the quality of the bone. At fundamental properties, the bone is harder. This loss of elasticity of the bone infuses on its capacity to absorb energy and therefore decreases the tenacity of the bone (capacity of the bone to resist to the propagation of cracks): these are antagonistic properties. At the structural level, a change in the structure of the bone is observed. This results in a loss of bone heterogeneity leading to micro-osteopetrosis or even sclerosis of the bone [32]. Moreover, this sclerosis, encountered on radiological examination in our series, is a sign of the change in the mechanical properties of the alveolar bone around the implant (Figs. 4 and 5).

These changes in the mechanical properties of the bone make it susceptible to micro-fractures occurrence. Due to the decrease in bone remodeling, the repair of micro-fractures decreases and an accumulation of microfractures occurs. The microfractures, which on the one hand make the bone even more fragile, and on the other hand constitute an entry point for infections, could actively participate in the development of MRONJ related to implants [33].

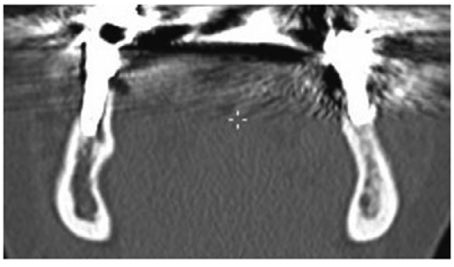

Fig. 5. CT-scan image showing a mandibular sclerosis localized around the implant 37 having developed a MRONJ.

Implant rehabilitation changes the biomechanical harmony of the manducatory system in several ways.

- The patient's gnathological elements (the number of implants, the connectivity, the number of remaining teeth, bruxism, jaws relationship. . .) can directly influence the implant overload.
- This deformation of the jaw during physiological chewing movements tends to concentrate stresses on the implants more than on the teeth [34].
- The fact that dental implants do not have a periodontal ligament means that there is a change in the transmission of forces. This leads to a loss of stress absorption, neurological sensation (desmoperception) and the ability to change position, all of which concentrate stress on the bone around the dental implants. These stresses can become high enough to cause localized bone necrosis in this group of implant patients [17].

It is difficult to collect data concerning the mechanical component in the etiology of implant-related MRONJ because they require an extensive biomechanical study for each patient. Moreover, patients are not comparable to each other regarding their oral situation (the number of implants, the connectivity, the number of remaining teeth, bruxism, jaws relationship. . .). This limits the accumulation of evidence on this subject.

Our results illustrate this clinical entity: MRONJ linked to the presence of implants. Being aware of the limitations by a small number of patients and the retrospective approach, we can see that:

- In general, MRONJ around implant is a rare event and concerns only 6 patients out of the 168 in the cohort (3.57%). But in the cohort, only 12 patients haveimplant(s) (7.14%), which means that 50% of patients with MRONJ and implant(s) had MRONJ related to their implant(s), what is more questionable. Obviously, the results must be qualified with the low number of patients with implant(s) and MRONJ.
- In our study, all cases were related to IPTO, such as in the literature.
- All patients received multiyear therapy with ARDs ranging from 2 to 5 years.
- All patients received IV or SC ARD administration (which is consistent with the literature).In our series, the upper jaw was more commonly affected (which is in contradiction with the literature).
- Fifteen of the 17 implants were posterior implants. This is in accordance with the observation of Jacobsen et al. [11]. This phenomenon is probably secondary to the greater stress in posterior jaw and the more difficult plate control.

Often, when more than one implant was present, MRONJ's foci tended to spread to the contiguous implants.

- In two patients, only one implant was involved. This tendency to multiple implant failures known in the literature as the "cluster phenomenon" has already been described by Martin et al. [35] and may raise suspicion of genetic risk factors [36]). The role of the microbiome could be a hypothesis.
- Not exceptionally, there were visible structural changes in the bone on the CT scan (osteosclerosis, loss of the heterogeneity).
- Not exceptionally, there was an infectious/traumatic focus in the vicinity of the MRONJ focus (indicative of poor oral hygiene status).
- Finally, the principle of treatment of MRONJ linked to the implant has not change compared to the classic MRONJ.
- In all cases, MRONJ lesions were stabilized or even healed.

- The large difference between the number of implants in the osteoporotic and oncologic group can be explained by the small sample size of the series as well as by the fact that oncologic patients could have a too short follow-up before developing MRONJ around their implants.

5. Conclusion

In conclusion, implant-related MRONJ (like classical MRONJ) is a rare entity with devastating complications for the patient. It should be considered a late complication of implant therapy and the patient must be informed of this side effect.

Our series illustrates the IPTO even if the implants are inserted before the ARD's therapy.

Although still poorly understood, the etiological elements of IPTO should draw our attention to the prevention of MRONJ.

The majority of studies are retrospective and long-term prospective studies are needed to study implant-related MRONJ.

A rigorous initial assessment with analysis of the peri-implant parameters and the biomechanical harmony of the manducatory system are the base for decision to remove an implant or not before the initiation of ARD.

The patient's motivation to maintain a good oral condition is a key element in the prevention of MRONJ. A regular follow-up (every 3 months) of the implants and oral condition is needed.

Declaration of Competing Interest

The authors declare that they have no competing interest.

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