

Drug-induced osteonecrosis of the jaw: the state of the art

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SUMMARY

Osteonecrosis of the jaw (ONJ) is a rare adverse event of antiresorptive drugs such as bisphosphonates (BP) and denosumab (DMAb).

The diagnosis of ONJ is considered in cases where exposed bone in the maxillofacial region does not heal within 8 weeks in a patient previously treated with an antiresorptive agent. In patients with osteoporosis, ONJ is reported as a very rare adverse event while in oncologic patients with bone metastases or malignant hypercalcemia the incidence is significantly higher (up to the 1-10% of the patients). The pathophysiology of ONJ is still not completely understood but it is multi-factorial. ONJ is a condition associated with poor oral health, oral surgery, and use of antiresorptive agents. Prevention is of paramount importance especially in cancer patients, in whom the large majority of cases of ONJ (>90%) are reported, but it should also be considered in osteoporotic patients, especially during dental surgical procedure. Some simple prevention procedures are effective in reducing the risk of its appearance. When ONJ unfortunately occurs, the large majority of patients can be managed conservatively.

In conclusion, ONJ is a rare condition associated with antiresorptive drugs. Both osteoporotic and oncologic patients should be well informed about its low absolute risk and regarding the fact that the benefits of antiresorptive therapy far outweigh this potential risk of ONJ.

Key words: Osteonecrosis of the jaw; bisphosphonates; osteoporosis.

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■ INTRODUCTION

Osteonecrosis of the jaw (ONJ) is a rare condition and a possible adverse event of bisphosphonates (BP) or denosumab (DMAb). It was reported for the first time in 2003 (1), when 36 cancer patients receiving treatment with pamidronate or zoledronate developed a painful bone exposure of the mandible, of the maxilla or both, unresponsive to surgical and medical treatment. Since then, several case reports have been published as well as retrospective and limited prospective data, showing that more than 90% of the cases of ONJ occurred in oncologic patients who were receiving high doses of antiresorptive therapy (2).

■ CLINICAL DIAGNOSIS

The International Task Force on ONJ (3) defines ONJ as:

1. Presence of exposed bone in the maxillofacial region which does not heal within 8 weeks after identification by a health care provider;
2. Exposure to an antiresorptive agent (BP or DMAb);
3. No history of radiation therapy to the craniofacial region.

The diagnosis of ONJ can be made according to these clinical criteria only after the exclusion of other possible causes of odontalgia. Several more common diseases should be taken into account prior to suspecting an early phase of ONJ, such as periodontal or apical abscess, pulpitis, sinusitis, dental caries, mucosal ulceration or cancer, etc.

Patient history and clinical examination remain the most sensitive diagnostic tools. After a thorough evaluation, the persistence of exposed bone in the oral cavity for 8 weeks or longer without any response to

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appropriate therapy is the hallmark of ONJ. Findings on plain film imaging or on computed tomography (CT) are non-specific. The presence of areas of focal sclerosis, thickened lamina dura and reactive periosteal bone may only help the clinician to predict possible future sites of exposed necrotic bone (3). Plain films, CT, MRI, bone scanning, and positron emission tomography may also be useful in assisting the staging and the scheduling of surgical interventions (3).

■ STAGING

ONJ may remain asymptomatic for long periods, ranging from weeks to several months or years (3). For this reason, the International Task Force on ONJ recommended a specific staging, as reported in Table I and Figure 1 (3).

Some scientific societies (such as AAOMS: American Association of Oral and Maxillofacial Surgeons) proposed an early prodromal phase defined as stage 0, including individuals treated with antiresorptive therapy complaining of pain and with radiographic features of osteosclerosis (3). However, the Task Force agreed not to consider this stage 0 terminology, in order to avoid the risk that this fea-

Table I - ONJ staging recommended by Task Force.

Stage 1: disease is described as the presence of exposed bone in asymptomatic patients with no evidence of significant adjacent or regional soft tissue inflammation or infection.
Stage 2: disease is characterized by exposed bone in the oral cavity in association with pain, soft tissue swelling, or secondary infection.
Stage 3: disease is characterized by exposed bone in association with pain, soft tissue swelling, or infection as well as pathologic fracture or extra-oral fistula or oral antral fistula or radiographic evidence of osteolysis extending to the inferior border of the mandible or the floor of the maxillary sinus.

ture might lead to over-diagnosis of ONJ, since the same presentation of symptoms may be related to several alternative diagnoses (3) (Figure 1). Indeed, only about 50% of individuals with such lesions develop a real ONJ.

■ EPIDEMIOLOGY

When considering drug safety for the management of osteoporosis, ONJ is reported as a very rare adverse event (less than 1 case for every 1000 patients treated) associated with the use of BP and DMAB (4). In view of such a low incidence, it is not surprising that ONJ was not reported

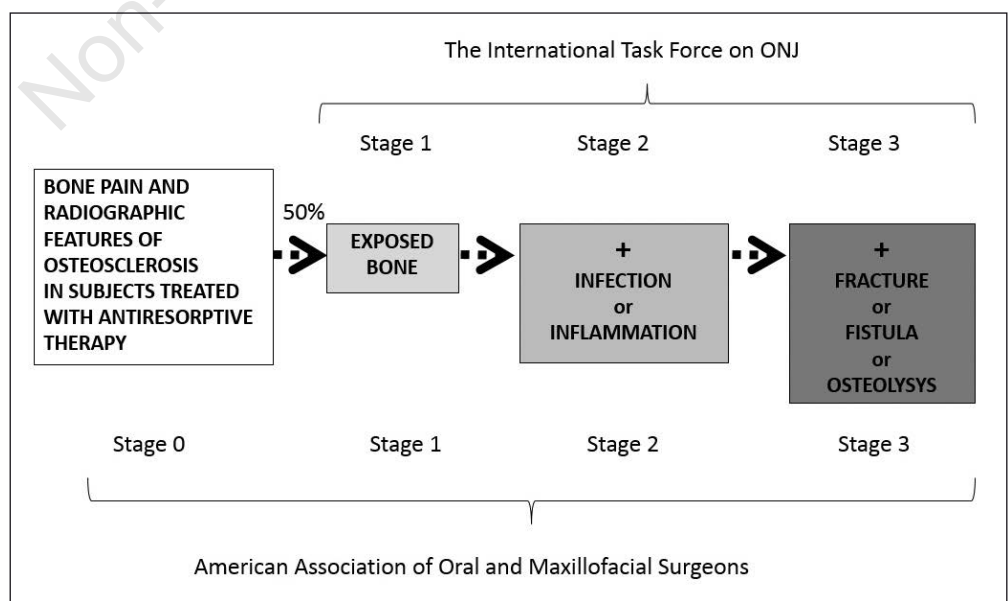


Figure 1 - Staging of ONJ according to different scientific societies.

for many years during pivotal osteoporosis BP studies. In addition, it could explain the difficulties in the accurate evaluation of the real incidence of the disease.

In the Health Outcomes and Reduced Incidence with Zoledronic Acid Once Yearly (HORIZON) pivotal fracture trial, involving 3889 patients, two cases of potential ONJ were identified (one in the placebo group and one in the zoledronic-acid group) (5).

In oncologic patients with bone metastases or malignant hypercalcemia, the context is very different, since they are exposed to a much more intensive osteoclast inhibition. These patients are usually treated with dosages ten times greater than those used for osteoporosis.

In this population the incidence of ONJ is more accurately estimated and appears to be significantly higher (up to 1-10% of the patients) (3, 6).

Recently some clinical trials, with an identical design, compared denosumab to zoledronic acid in the prevention of skeletal-related events (pathologic fracture, radiation therapy for the bone, bone and spinal cord compression) in over 5700 patients with breast cancer, prostate cancer, multiple myeloma or solid tumors with bone metastasis. The pooled data were also used to study the incidence, the risk factors and the outcomes of ONJ (7). In total, 89 cases of ONJ cases were documented and the incidence in the DMAB arm was 1.8% vs 1.3% in the zoledronic acid arm (a non-statistically significant difference) (7). With a such low incidence of ONJ, the benefit of the high-dose antiresorptive therapy largely outweighs the risk of ONJ by a factor of 17 (3).

The incidence of ONJ in cancer patients appears to be related to many factors such as the dose used, the duration of the treatment, the specific kind of malignancy (with a higher risk in patients with breast or prostate cancer or with multiple myeloma) (8).

Furthermore, the use of concurrent drugs potentially interfering with bone health should be considered (*i.e.* glucocorticoids or antiangiogenic drugs) (3).

■ RISK FACTORS

The lack of consistent epidemiological data concerning ONJ has made it very difficult to define the risk factors. The Task Force proposed the following risk factors as significant for the development of ONJ in the oncology population, in decreasing order of importance (3):

1. use of i.v. BP (both cumulative dose and duration of exposure impact ONJ risk);
2. use of DMAB (both cumulative dose and duration of exposure impact ONJ risk);
3. radiation therapy;
4. dental extraction;
5. chemotherapy;
6. periodontal disease;
7. use of oral BP;
8. osteoporosis;
9. local suppuration;
10. glucocorticoid therapy;
11. diabetes;
12. denture use;
13. erythropoietin therapy;
14. tobacco use;
15. hyperthyroidism;
16. renal dialysis;
17. cyclophosphamide therapy;
18. increasing age.

When the osteoporosis patient population was considered, the Task Force considered as significant a smaller number of risk factors for the development of ONJ, in decreasing order of importance (3):

1. suppuration;
2. use of BP (duration of treatment impact ONJ risk);
3. dental extraction;
4. anemia.

A previous paper (9) studied the most common items associated with non-cancer-related cases of ONJ and found that, similarly to the oncologic population, invasive dental procedures (*i.e.* tooth extraction, oral surgery) were the most common risk factor. In Italy dental implant is the most common cause for the discontinuation of osteoporosis treatment with BP or DMAB, even if there is currently no evidence for dental implant as a risk factor for ONJ even in cancer patients. Recent reviews also stat-

ed that successful implant therapy is possible in patients receiving antiresorptive therapy (10-12).

Among the concomitant medical issues besides periodontal disease or other oral conditions, rheumatoid arthritis and diabetes were also reported, while the most commonly used medication affecting bone metabolism was glucocorticoid therapy (9). Several effects of glucocorticoids may contribute to increased risk of ONJ, such as inhibition of the osteoblast function, increased osteoblast and osteocyte apoptosis, increased bone resorption, immunosuppression, impaired wound healing and increased risk of local infection (2).

■ PATHOPHYSIOLOGY

The relatively recent observation that not only BP but also DMAb may cause the appearance of ONJ made it necessary to research for the mechanisms common to both interventions. BP promote osteoclast apoptosis and deposit in the bone, where they persist for a long time. On the contrary, DMAb does not accumulate inside the bone and inhibits osteoclastic bone resorption without causing apoptosis (13). The pathophysiology of ONJ is not yet fully understood but it is certainly multifactorial (14). Here we report the main known mechanisms underlying this condition.

■ INFECTION

ONJ is a pathological condition occurring only in the jaw bones, which have certain precise anatomical and microbiological features that cannot be found in other bones of the body and that predispose them to bacterial infection (15):

1. the teeth erupt from the jawbone, breaking through the oral epithelium and allowing infectious agents residing in the oral cavity to invade the jawbone via the gap between the epithelium and the teeth or via the root canal;
2. the oral mucosa covering the jawbone is thin, and thus infection caused by mucosal injury can spread to the jawbone beneath the mucosa;

3. more than 800 types of resident bacteria inhabit dental plaque and can represent a source of infection in the oral cavity;
4. inflammation due to tooth decay, pulpitis, periapical lesions, or periodontal disease extends to the jawbone;
5. the jawbone is exposed to the oral cavity following invasive dental treatments including tooth extraction, leading to infection.

The major histopathological finding in ONJ is chronic osteomyelitis accompanied by osteonecrosis (15). Actinomyces colonies (resident bacteria in the oral cavity) are frequently found in contact with necrotic bones in ONJ lesions, supporting the possibility that Actinomyces bacteria could play a key role in the pathogenesis of ONJ (16). Bacteria also stimulate bone resorption through the production of local cytokines and contribute to bone necrosis.

In this context, there is evidence that the occurrence of ONJ is significantly reduced by the treatment of the oral infection via extensive oral health control, thus suggesting that infection is a key step towards the development of ONJ (3, 15).

■ SUPPRESSION OF BONE TURNOVER

Even though BP and DMAb, both potent antiresorptive drugs, have different molecular mechanisms of action, both are associated with ONJ. Thus, it is quite natural to consider the suppression of bone resorption and of bone turnover as possible mechanisms in the development of ONJ.

Furthermore, the risk of ONJ increases with both the cumulative dose and the duration of exposure to the treatment (2, 3, 15). This pathogenetic hypothesis would explain the appearance of ONJ through an excessive inhibition of bone remodeling and therefore resulting in an impaired osteoclast activity, too inadequate to allow the healing of the extraction socket (2). The studies cited above are consistent with this hypothesis, although ONJ has never been reported in other conditions associated with low bone turnover.

Very recently, two cases of ONJ have also

been reported in patients treated with romosozumab (17). Romosozumab is a monoclonal antibody that binds sclerostin and acts as a potent bone anabolic agent. This drug increases bone formation but also decreases bone resorption at the same time (17). This latter effect might possibly explain the development of ONJ.

■ BONE/MUCOSAL INJURY

We have already discussed the predisposition of jaw bones to bacterial infections. Obviously, any cause of injury to the oral mucosa and/or the bone can contribute to infection, therefore infections themselves can contribute to further mucosal damage. This fact explains why invasive dental procedures (*e.g.* tooth extraction, oral surgery) are the most common risk factors for ONJ (3, 9). In the same way, other risk factors may also be responsible for reducing the mucosal defenses: glucocorticoids, tobacco use, diabetes, rheumatoid arthritis, radiation and chemotherapy, etc.

■ VASCULARITY

The possible role of a deficit in vascularity has been hypothesized, since ONJ has been also described in some cancer patients treated with antiangiogenic agents such as sunitinib and bevacizumab (3, 15), though all these patients had other risk factors for ONJ. BP are known to have antiangiogenic properties although animal studies with these drugs do not support any diminution of the vascular volume associated with their administration (3). DMAB is currently not known to have any antiangiogenic effect.

■ GENETICS

We still do not know why, given that millions of patients take antiresorptive drugs and have similar risk factors, only such a small number of them develop ONJ. It has been suggested that polymorphisms in the farnesyl pyrophosphate synthase (18) or cytochrome *P450 CYP2C8* genes (19) could predispose some individuals to ONJ.

■ PREVENTION

As previously discussed, ONJ is a condition associated with poor oral health, oral surgery, and use of potent antiresorptive agents. In the attempt to prevent ONJ, optimizing oral health prior to the initiation of BP and DMAB therapy is emphasized and it has been proven to be effective in reducing its risk (3).

Recommendations include (3):

1. completion of necessary oral surgery prior to the initiation of antiresorptive therapy;
2. administration of antibiotics 2-4 days before and 7-10 days after the procedure;
3. antimicrobial mouth rinsing;
4. appropriate closure of the wound following tooth extraction;
5. maintenance of good oral hygiene.

The large majority of cases (>90%) of ONJ have occurred in cancer patients. Therefore it is recommended by the Task Force (3) that when these patients undergo invasive oral surgery, their antiresorptive therapy should be withheld until soft tissue healing has occurred, even though there is no evidence supporting this recommendation in terms of changing the outcome of the dental procedure. Since the pharmacological effects of DMAB are transient and reversible, this recommendation could in any case be useful. On the contrary, since BP are characterized by long-term skeletal retention, discontinuation of the treatment is not expected to have a significant and immediate impact on bone remodeling. However, since the uptake of BP is considerably increased at sites of local bone injury, withholding the therapy after oral surgery may reduce the local deposition of the drug in the jaw bones.

In patients taking lower doses of antiresorptive therapy for osteoporosis, the risk of ONJ is extremely low and thus the discontinuation of oral BP is not essential prior to dental procedures, especially in patients with higher fracture risk (3, 20). In conclusion, in order to identify the best approach for each patient with concurrent antiresorptive treatment, it is necessary

to stratify the risk of ONJ and to weigh it against the risk of osteoporotic fracture and/or the risk of skeletal-related events in cancer patients.

■ MANAGEMENT

The large majority of patients with ONJ can be managed conservatively (optimal oral hygiene, regular professional dental care, elimination of active dental and periodontal disease, topical antibiotic mouth rinses and systemic antibiotic therapy). Teriparatide may be considered a conservative treatment choice for those with osteoporosis and without cancer or prior radiation therapy to bone (2, 3, 21). Subjects with stage 3 ONJ may be considered for surgery with osteotomy of the affected area (2, 3).

■ CONCLUSIONS

ONJ is an uncommon condition associated with antiresorptive treatment and with multiple further factors contributing to its pathophysiology. The large majority of cases (>90%) occur in cancer patients and simple prevention procedures are effective in reducing its risk.

Both osteoporotic and oncologic patients should be well informed about ONJ but also well reassured as to its low absolute risk and also correctly advised regarding the fact that the benefits of antiresorptive therapy far outweigh the potential risk of ONJ.

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