*The Journal of Clinical Endocrinology & Metabolism*, 2022, **107**, 1441–1460
https://doi.org/10.1210/clinem/dgab888
Advance access publication 18 December 2021
**Reports and Recommendations**

# Osteonecrosis of the Jaw and Antiresorptive Agents in Benign and Malignant Diseases: A Critical Review Organized by the ECTS

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## Abstract

**Context:** Antiresorptive therapy significantly reduces fracture risk in patients with benign bone disease and skeletal-related events (SREs) in patients with bone metastases (BM). Osteonecrosis of the jaw (ONJ) is a rare but severe condition manifested as necrotic bone lesion or lesions of the jaws. ONJ has been linked to the use of potent antiresorptive agents, termed *medication-related ONJ* (MRONJ).

**Objective:** We aimed to identify the differences various aspects of MRONJ among distinct patient categories and provide recommendations on how to mitigate the risk and optimally manage MRONJ in each of them.

**Methods:** A working group of the European Calcified Tissue Society (ECTS) and 2 experts performed an updated detailed review of existing literature on MRONJ incidence, characteristics, and treatment applied in bone diseases with variable severity of skeletal insult, ranging from osteoporosis to prevention of cancer treatment–induced bone loss and SREs in cancer patients with BM.

**Results:** The risk for MRONJ is much higher in patients with advanced malignancies compared to those with benign bone diseases because of the higher doses and more frequent administration of antiresorptive agents in individuals with compromised general health, along with coadministration of other medications that predispose to MRONJ. The overall risk for MRONJ is considerably lower than the benefits in all categories of patients.

**Conclusion:** The risk for MRONJ largely depends on the underlying bone disease and the relevant antiresorptive regimen applied. Physicians and dentists should keep in mind that the benefits of antiresorptive therapy far outweigh the risk for MRONJ development.

**Key Words:** bisphosphonates, bone metastases, denosumab, osteonecrosis of the jaw, osteoporosis

**Abbreviations:** AAOMS, American Association of Oral and Maxillofacial Surgeons; AI, aromatase inhibitor; ALN, alendronate; ARONJ, antiresorptive agent–related osteonecrosis of the jaw; BM, bone metastases; BMA, bone-modifying agent; BP, bisphosphonate; BRONJ, bisphosphonate-related osteonecrosis of the jaw; CLO, clodronate; CTIBL, cancer treatment–induced bone loss; Dmab, denosumab; DRONJ, denosumab-related osteonecrosis of the jaw; ECTS, European Calcified Tissue Society; IBN, ibandronate; IV, intravenous; MM, multiple myeloma; MRONJ, medication-related osteonecrosis of the jaw; ONJ, osteonecrosis of the jaw; OP, osteoporosis; OPG, orthopantomography; PAM, pamidronate; QoL, quality of life; RIS, risedronate; RLX, raloxifene; SRE, skeletal-related event; TKI, tyrosine kinase inhibitor; TPTD, teriparatide; VEGF, vascular endothelial growth factor; ZOL, zoledronate.

An imbalance of bone turnover, with relatively increased osteoclast-mediated bone resorption rate, characterizes a broad spectrum of bone diseases, ranging from osteoporosis (OP) and other benign bone diseases to cancer treatment–induced bone loss (CTIBL; aromatase inhibitor (AI)-induced bone loss, and androgen deprivation–induced bone loss) and bone metastases (BM) in advanced malignancies. In all these conditions, targeting the osteoclast with antiresorptive agents is currently the cornerstone of treatment of the respective bone disease. Among them, bisphosphonates (BPs), and denosumab (Dmab) are the more potent and more frequently used agents in everyday clinical practice.

BPs are divided into oral, including alendronate (ALN), risedronate (RIS), clodronate (CLO), and ibandronate (IBN), and intravenous (IV) agents, including IBN, pamidronate (PAM), and zoledronate (ZOL). In general, oral BPs are preferred in OP and other benign bone diseases, whereas for prevention of CTIBL and the management of BM, IV BPs are mostly used (Table 1). Dmab binds the receptor activator of nuclear factor κ-B ligand (RANKL), thus inhibiting osteoclast differentiation, function, and survival (1). BPs and Dmab

**Received:** 5 November 2021. **Editorial Decision:** 8 December 2021. **Corrected and Typeset:** 6 January 2022

both significantly decrease the risk of vertebral (by 41%-77% and 68%, respectively) and hip (by 30%-51% and 40%, respectively) fractures in OP patients (2, 3) and the incidence of skeletal-related events (SREs) in cancer patients (4, 5). The regimen of each BP and of Dmab varies depending on the disease (see Table 1).

## Osteonecrosis of the Jaw: Definitions and Staging

### Description

Osteonecrosis of the jaw (ONJ) is a rare but serious condition manifested as one or more necrotic bone lesions that are exposed or can be probed through an intraoral or extraoral fistula in the maxillofacial region, and persist for at least 8 weeks without response to appropriate therapy (6, 7). ONJ is more commonly located in the mandible (8-10) but can be detected at both jaws (10). It may be accompanied by pain, inflammation, erythema, suppuration, and loose teeth. Although ONJ may occur spontaneously, in most cases it is the result of a dental procedure, for example, a tooth extraction or oral surgery (9, 11). Dentoalveolar infections may precede the appearance of necrotic bone (9). Lack of history of radiation therapy or metastatic disease to the jaws is required to confirm the diagnosis of ONJ (6).

### Terminology

The occurrence of ONJ was initially associated with BP administration, and named *bisphosphonate-related ONJ* (BRONJ) (12). Later, ONJ was also attributed to Dmab (DRONJ), and named *antiresorptive agent–related ONJ* (ARONJ), and afterward to antiangiogenic medications and tyrosine kinase inhibitors (TKIs), transforming the term to the currently used *medication-related ONJ* (MRONJ) (6). To date, several other medications, mostly used in the oncology setting, have also been linked to the risk of MRONJ (9, 13) (Table 2).

### Staging

Among several proposals for staging of ONJ (11), the staging of the American Association of Oral and Maxillofacial Surgeons (AAOMS) is now most commonly used (6) (Table 3). A nonexposed variant was also introduced (14), and not including this variant is reported to considerably underdiagnose ONJ (15).

## Aim

The ECTS considers that there is confusion among clinicians and dentists regarding the occurrence and optimal prevention/management of ONJ, possibly owing to discrepancy regarding definition, incidence, characteristics, and treatment. This may in part relate to the underlying bone disease and consequent regimen (doses and frequency) of the antiresorptives administered. Therefore, we attempt to clarify various aspects of ONJ among patients with OP in comparison to patients at risk for CTIBL and patients with BM or multiple myeloma (MM). We provide recommendations on how to mitigate risk and optimally manage ONJ in each of these patient categories.

## Methods

This review was performed under the auspices of the Clinical Action Group of the Policy and Consensus Committee of the ECTS. Detailed methodology is quoted in the Supplementary data (16). This review was not set up to make grade-based recommendations; given the lack of high-quality data, evidence would most likely be low, and this would render grade recommendations weak. The final manuscript has not been subjected to a membership hearing but has been approved for submission by the board of directors of the ECTS.

## Pathophysiology

Several mechanisms have been proposed to contribute to MRONJ, with oversuppression of bone turnover considered the main mechanism attributed to antiresorptives. Infection and inflammation, as well as angiogenesis inhibition, are also important factors predisposing to ONJ development.

### Inhibition of Bone Resorption and Turnover—Good for the Bone, Bad for the Jaw?

Bone turnover suppression is the main mechanism by which antiresorptives increase bone density and reduce fracture risk. However, osteoclast differentiation and functionality, and a degree of bone remodeling, is crucial for bone healing and repair of microdamage. Interestingly, "osteonecrosis" occurs primarily within the alveolar bone of the jaws and not in other skeletal sites. A comparatively higher remodeling rate in the jaws compared to other bones may play a role in this predisposition (17). Repetitive microtraumas from chewing

**Table 1.** Regimen of antiresorptive agents according to underlying bone disease

| | Osteoporosis | | CTIBL | | Bone metastases | |
|---|---|---|---|---|---|---|
| | Dose | Frequency | Dose | Frequency | Dose | Frequency |
| **Bisphosphonates** | | | | | | |
| Alendronate | 70 mg by mouth | Weekly | 70 mg by mouth | Weekly | – | – |
| Risedronate | 35 mg (75 mg) by mouth | Weekly (2 consecutive d/mo) | 35 mg by mouth | Weekly | – | – |
| Ibandronate | 150 mg by mouth | Monthly | 150 mg by mouth | Monthly | 50 mg | Daily |
| | 3 mg IV | Every 3 mo | – | – | 6 mg IV | Every 3-4 wk |
| Pamidronate | – | – | 60 mg IV | Every 3 mo | 90 mg IV | Every 3-4 wk |
| Zoledronate | 5 mg IV | Yearly | 4 mg IV | Every 3-6 mo | 4 mg iv | Every 3-4 wk[a] |
| **Denosumab** | 60 mg SC | Every 6 mo | 60 mg SC | Every 6 mo | 120 mg SC | Every 4 wk |

Abbreviations: CTIBL, cancer treatment–induced bone loss; IV, intravenously; SC, subcutaneously.
[a]At least for the first 3 to 6 months; de-escalation to doses every 12 weeks could be considered thereafter.

**Table 2.** Nonantiresorptive medications associated with osteonecrosis of the jaw development

| Class | Representatives |
|---|---|
| Glucocorticoids | |
| VEGF inhibitors | Bevacizumab, aflibercept |
| TKIs | Sunitinib, imatinib, cabozantinib, sorafenib, regorafenib, axitinib, pazopanib, dasatinib |
| mTORi | Everolimus, temsirolimus |
| BRAF inhibitors | Dabrafenib, trametinib |
| Monoclonal Abs against CD20 | Rituximab |
| Immune checkpoint inhibitors | Nivolumab, monoclonal Abs against CTLA-4 (ipilimumab) |
| Lenalidomide | |
| Chemotherapy regimens | Cytarabine, idarubicin, and daunorubicin; gemcitabine, vinorelbine, and doxorubicin; doxorubicin and cyclophosphamide; 5-azacitidine |
| Leflunomide | |
| Anti-TNF agents | Adalimumab |

Abbreviations: Abs, antibodies; BRAF, B-Raf; CTLA-4, cytotoxic T-lymphocyte–associated protein 4; TKIs, tyrosine kinase inhibitors; mTORi, inhibitors of mammalian target of rapamycin; TNF, tumor necrosis factor; VEGF, vascular endothelial growth factor.

**Table 3.** Staging according to the American Association of Oral and Maxillofacial Surgeons and the alleged nonexposed variant

| Stage | Description |
|---|---|
| At risk | Patients treated with bone-modifying agents but without apparent necrotic bone (eg, all asymptomatic patients treated with antiresorptives) |
| Stage 0 | No clinical evidence of necrotic bone but nonspecific symptoms or clinical/radiographic findings |
| Stage 1 | Exposed and necrotic bone, or fistulae that probe to bone, that are asymptomatic with no evidence of significant adjacent or regional soft-tissue inflammation or infection |
| Stage 2 | Exposed and necrotic bone, or fistulae that probe to bone, associated with infection, evident by pain and adjacent or regional soft-tissue inflammatory swelling, with or without purulent drainage |
| Stage 3 | Exposed and necrotic bone, or fistulae that probe to bone, associated with pain and infection, and at least one of the following: (1) pathologic fracture, (2) extra-oral fistula, (3) oral-antral fistula, or (4) radiographic evidence of osteolysis extending to the inferior border of the mandible or floor of the maxillary sinus |
| Nonexposed variant (not widely adopted) | Presence of otherwise unexplained pain in the jaws, fistula, swelling, mobile teeth, or mandibular fracture diagnosed after excluding common diseases of the jaw known to cause similar manifestations |

may also contribute. Additionally, jaw osteoclasts may absorb higher amounts of BPs than long bone osteoclasts (18). Indirect evidence of the pivotal role of bone turnover suppression in MRONJ development derives from the facts that MRONJ has almost exclusively been attributed to the most potent antiresorptives and is far more common among BM or MM patients, for whom higher doses are administered in more frequent intervals, compared to OP. Additional, indirect, evidence comes from the improved extraction socket healing and resolution of ONJ when parathyroid hormone was administered in animals (19-21) and humans (22, 23).

## Local inflammation and infections

Periodontal or periapical disease was common in initially reported cases (24). Subsequently, animal models proved that inflammation or bacterial infection combined with antiresorptives can induce ONJ (25, 26). A complex biofilm, composed of bacteria, especially *Actinomyces* species (10, 27), along with fungi and viruses (28), has been identified in biopsies of necrotic bone from ONJ lesions. Increased local infections and impaired oral mucosa healing with BPs suggested a synergistic role of antiresorptives with inflammation and infection (29, 30). BP administration has been associated with proliferation and adhesion to hydroxyapatite of oral bacteria (31). Furthermore, BPs may impair the immune response to infection through activation of γ δ T cells and altered production of proinflammatory cytokines (32).

## Angiogenesis inhibition

Angiogenesis requires binding of signaling molecules, such as vascular endothelial growth factor (VEGF), to their receptors on endothelial cells, and is considered vital for tumor growth and metastases. VEGF inhibitors are used by oncologists to deter tumor growth. Osteonecrosis, which is an avascular necrosis, entails interruption of the blood supply in the lesion. Administration of antiangiogenic agents, for example, antibodies targeting VEGF and TKIs, has been linked with ONJ occurrence (11). Additionally, glucocorticoids, especially in the high doses used in the oncology setting, exert antiangiogenic effects (33). High doses of potent BPs, especially ZOL, have been consistently associated with decreased angiogenesis according to in vitro studies (34, 35) and decreased VEGF levels in human studies (36, 37). On the contrary, there is no evidence that Dmab exerts antiangiogenic effects (35).

## Immune system dysfunction

Accumulated indirect evidence suggests that dysregulation of the immunological response may contribute to MRONJ development. The higher MRONJ occurrence when glucocorticoids are coadministered with BPs both in animals (38, 39) and

humans (7) has been attributed to the immunomodulating effects of glucocorticoids on T-cell subpopulations (39), whereas immunotherapy with mesenchymal stem cells prevented and even cured MRONJ (39). Besides glucocorticoids, concurrent chemotherapy increases MRONJ risk (7), as do other conditions that adversely affect the immune system, including diabetes, inflammatory joint diseases, and even compromised general health (7). In addition, anti-VEGF agents can inhibit macrophage chemotaxis (40) while anti-TKIs inhibit the differentiation of cells of the monocyte/macrophage lineage, conditioning the local response of the immune system (41). Biologic immunomodulators, including anti–tumor necrosis factor α, anti-CD20, mammalian target of rapamycin inhibitors, and methotrexate have also been linked with ONJ development through their effects on immune system function (11). Finally, BPs and Dmab by themselves may affect monocyte and macrophage function and survival, although so far this has not been linked to systemic changes in immune function (41, 42).

### Soft-tissue toxicity

Besides their effect on osteoclasts, BPs decrease proliferation and increase apoptosis of several cell lines in vitro, disrupting the mucosal barrier and favoring bacteria invasion (43-45). Furthermore, BPs can suppress the migration of oral epithelial cells, a step crucial for tooth socket closure (31). It has been proposed that BPs accumulate in the jawbone in concentrations toxic to the oral epithelium, deterring healing of soft-tissue injuries caused by invasive dental procedures or even subclinical trauma from dentures (46). In contrast, no soft-tissue toxicity has been reported with Dmab.

### Vitamin D deficiency and osteomalacia

There is weak evidence for a role of vitamin D deficiency in MRONJ development. Studies have shown associations with chronic periodontitis or caries risk (47). Low vitamin D levels have been associated with ONJ in some (48, 49) but not all studies (50). Treatment with BPs in the presence of osteomalacia could exaggerate a mineralization defect (51). Such a mineralization defect has been described in ONJ patients (52).

### Genetic predisposition

Variants of several genes, including the cytochrome P450 CYP2C8 (53, 54), *VEGF* (54, 55), peroxisome proliferator-activated receptor γ (56), aromatase (57), farnesyl pyrophosphate synthase (58), the RNA-binding motif, single-stranded-interacting protein 3 (*RBMS3*) gene (59), insulin-like growth factor-binding protein 7 (*IGFBP7*) (59), the ATP-binding cassette subfamily C member 4 (*ABCC4*) gene (59), and sirtuin 1 (*SIRT1*) (60) genes have been associated with increased MRONJ incidence in genome-wide association studies and whole-exome sequencing analyses conducted mainly in cancer patients treated with BPs. However, none of these studies determined which gene polymorphisms present some association (61), while subsequent candidate gene studies failed to replicate these results, thus questioning the predictive role of these polymorphisms in the risk for MRONJ development (62).

### Pathophysiological mechanisms of medication-related osteonecrosis of the jaw related to underlying disease or antiresorptive agent

The pathogenesis of MRONJ is probably multifactorial. It is unclear if and which of the aforementioned mechanisms contribute the most to MRONJ development. Coexistence of more than one of the mechanisms seems to increase the risk. It is possible that the prevailing pathophysiological mechanism differs between BPs and Dmab, for example, the latter exerts no antiangiogenic effects or soft-tissue toxicity.

MRONJ is far more common in cancer patients compared to patients treated for benign bone diseases, such as OP (63). This is most likely a result of more intense and prolonged suppression of bone turnover by the higher and more frequent dosing, but may also be due to concurrent therapies (glucocorticoids, chemotherapy, antiangiogenic agents, immunomodulators) and decreased oral and general health in cancer patients (63).

### Osteonecrosis of the jaw cases without antiresorptive therapy

ONJ has been rarely but increasingly described in patients not receiving bone-modifying agents (BMAs) (7, 9, 10, 13). Oral ulceration and benign sequestration, a benign, transient condition of presently unknown incidence, manifests as painful ulceration usually over the posterior lingual mandible in the absence of systemic disease or prior use of antiresorptive or antiangiogenic therapy (64). It resolves spontaneously in a few days to several months (65-68), although it may persist for more than 8 weeks and be misdiagnosed as ONJ.

The non-BMA agents that have been associated with ONJ development, mainly in patients with malignancies, are quoted in Table 2. Cases of ONJ in noncancer patients receiving none of the previously mentioned agents have been sparsely reported (69).

## Incidence and Risk Factors

### Medication-related Osteonecrosis of the Jaw Associated With Bisphosphonate Use

MRONJ real incidence is difficult to ascertain because diagnosis of BRONJ followed different definitions until 2007, when the AAOMS proposed a definition of MRONJ, partially revised in 2009 and again in 2014 (6, 70, 71).

As already mentioned, the incidence of BRONJ is considerably lower in OP patients compared to cancer patients. Of note, in such populations (mainly postmenopausal women) numerous clinical trials, corresponding to more than 60 000 patient-years, have reported no incidence of BRONJ (72). According to the latest consensus, BRONJ incidence in OP patients ranges from 0.01% to 0.06% (6, 73, 74), although the incidence in Asia may be higher (75-77), maybe due a higher prevalence of periodontal disease.

On the contrary, in cancer patients, in whom the use of BPs aims to prevent CTIBL, decrease the incidence of SREs, and reduce the risk of BM, the reported frequency for MRONJ after ZOL ranged from 1% to 8% when used for BM, and from 0% to 1.8% when administered as adjuvant treatment (78). Probably the most important factor for this difference is the higher (~ 12-15 times) dose of BPs used for metastatic bone disease compared to OP, including, in the case of ZOL, the higher number of infusions (79-87). A possible bias in interpreting the difference in incidences among studies may arise from the different duration of follow-up of each study, which may be a potential confounder. In addition, even among cancer patients, MRONJ incidence was quite different when ZOL was administered in doses used for CTIBL prevention, compared with the higher cumulative doses used

for treatment of BM. Several local risk factors predispose to ONJ development (Fig. 1), the most common being tooth extraction. In cancer patients, tooth extraction not only after but also before initiation of BMA has been associated with MRONJ development (88). However, some studies suggest that preexisting dental disease, rather than tooth extraction, is the risk factor (88-93). In a recent systematic review, a 10% risk of MRONJ was noted in patients with periodontal disease treated with BPs (6). As expected, coexistence of local infection (periodontal/periapical inflammation) and tooth extraction further increases the risk of MRONJ (94). Systemic risk factors such as type of disease and concomitant therapies (eg, chemotherapy, glucocorticoids, antiangiogenic agents) also increase MRONJ risk (93, 95-110) (see Fig. 1). Among them, glucocorticoids, especially in the high doses used in oncology, alone or in combination with other medications, represent a prominent risk factor. Smoking (111-113), age (88, 97, 114), sex (74, 114), diabetes mellitus (112, 115), and obesity (111) have also been associated with ONJ risk, especially in oncology.

Despite the initial enthusiasm regarding the role of markers of bone resorption in the prediction of MRONJ risk, a systematic review suggested that no marker is useful in this setting (116).

Recently, a decline in the incidence of BRONJ has been reported, probably due to prevention of clinical risk factors. A 9-year (2009-2018) survey showed that the number of new MRONJ cases was stable from 2009 to 2015, with a mean of 51.3 cases per year declining during the years 2016 to 2018 to 33.3 cases per year (117). Increased clinician awareness as well as the reluctance of dental practitioners to perform dental procedures in patients on antiresorptives may have contributed to this decline in the incidence of ONJ.

## Medication-related Osteonecrosis of the Jaw Associated With Denosumab Use

Similarly to BPs, the incidence in OP patients is considerably lower than in cancer patients and risk factors appear identical (63, 118-129). A systematic review of randomized controlled trials that directly compared Dmab with BPs in postmenopausal women with OP identified no reports of MRONJ (126), whereas in the FREEDOM and FREEDOM extension study the incidence of MRONJ was 5.2 per 10 000 patient-years (130). According to the FAERS database, Dmab-treated OP patients had an odds ratio of 0.63 (95% CI, 0.56-0.70; $P < .001$) to develop MRONJ compared to untreated OP patients, whereas in contrast the odds ratio was 4.9 (95% CI, 4.4-5.4; $P < .001$) for cancer patients treated with Dmab for prevention of SREs compared to untreated cancer patients (131). Similarly, according to the Multinational Association of Supportive Care in Cancer report, in cancer patients treated with Dmab, MRONJ frequency ranged from 0.7% to 6.9% for BM, whereas in the setting of CTIBL it was 0% (78).

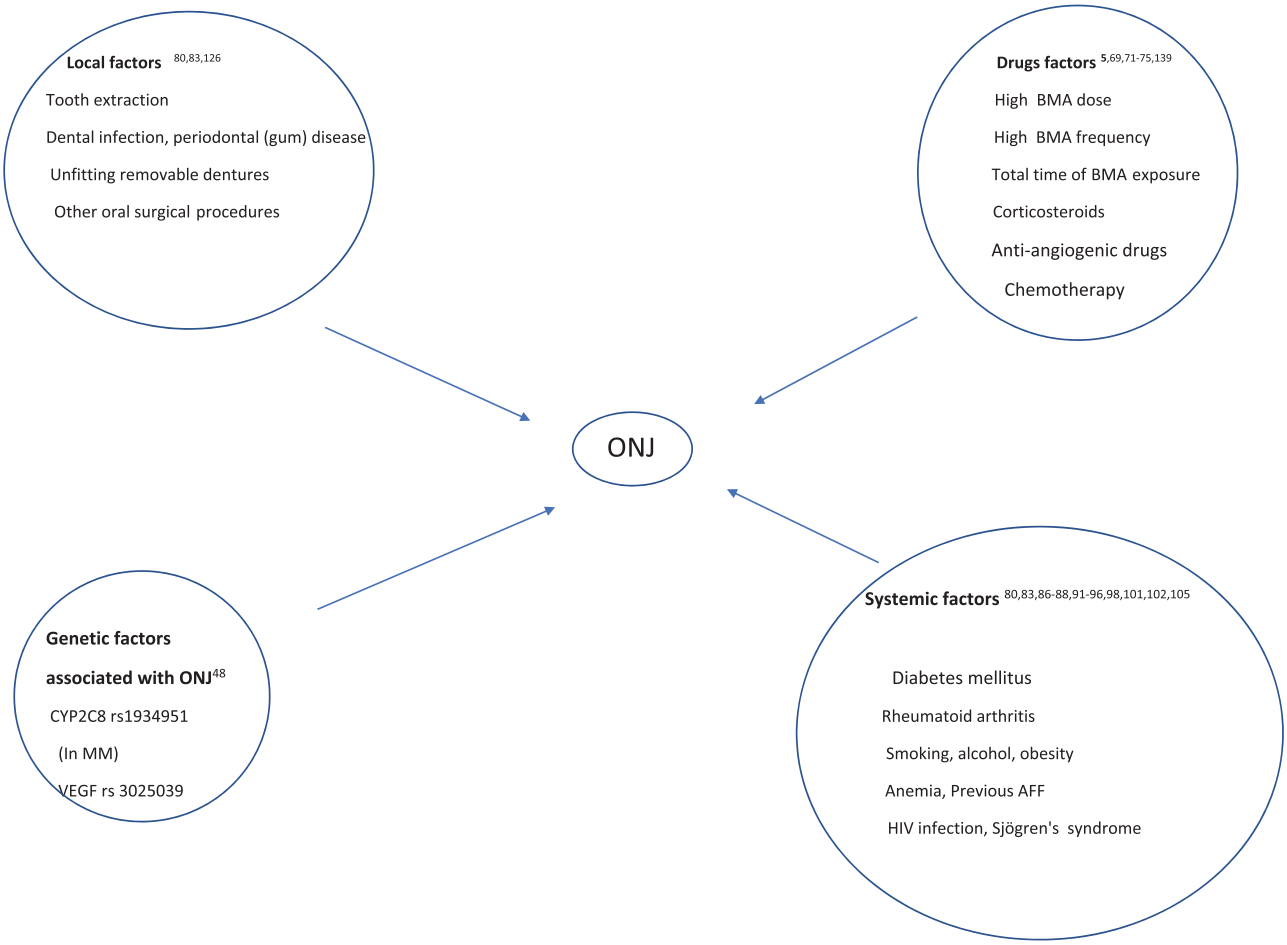


**Figure 1.** Risk factors for antiresorptive agent-related osteonecrosis of the jaw. AFF, atypical femoral fracture; BMA, bone-modifying agents; MM, multiple myeloma; ONJ, osteonecrosis of the jaw; VEGF, vascular endothelial growth factor.

Again, the incidence of MRONJ increases from cancer patients receiving Dmab for CTIBL, to those receiving Dmab for BM prevention, and finally those receiving it as BM therapy. In the CTIBL setting, where Dmab is administered in the same doses and frequency as administered for the treatment of OP, the incidence of MRONJ is similar to the incidence seen in OP patients, for example, no cases were reported in the latest double-blind, placebo-controlled trial, which included postmenopausal patients with early breast cancer (132). When Dmab was given monthly at a dose of 120 mg for the prevention of BM in prostate cancer patients, the incidence of MRONJ rose to 5% (133). The same incidence was reported in breast cancer patients in the D-Care trial (134).

Postmarketing surveillance data including 1 960 405 patient-years of Dmab exposure of 2 427 475 patients identified 47 adjudicated cases of MRONJ. All these individuals had at least one other risk factor for MRONJ development including concurrent glucocorticoid use, concurrent chemotherapy, prior BP use, or invasive dental procedures (74).

Frequently cancer patients switch BMA therapy, and a systematic review suggested an increased prevalence of MRONJ associated with sequential antiresorptive therapy with PAM and ZOL, and with BPs and Dmab when compared to single BMA therapy (135).

## Differences Among Antiresorptive Agents

MRONJ has been rarely reported with antiresorptive agents other than BPs or Dmab. Since the degree of bone turnover suppression is considered one of the main mechanisms of MRONJ development, "milder" antiresorptives, such as selective estrogen receptor modulators, may be an alternative for women at increased risk of ONJ with OP. Following the same concept, women with early-stage breast cancer receiving AIs to prevent CTIBL, could replace AIs with tamoxifen, weighing however the superiority of tamoxifen over AIs on bone density/fracture risk (136) with its inferiority on breast cancer outcomes (137). Only 1 out of 1869 Taiwanese OP patients treated with raloxifene (RLX) experienced ONJ compared to the 39 out of 6485 treated with ALN (138). Two more cases of ONJ with RLX have been reported, 1 after 4 years of RLX in a previously treatment-naive OP woman (139) and another after 18 months of RLX treatment, but in a woman with several comorbidities who had previously been treated with ALN for 2 years (140). No case of ONJ has been reported with other selective estrogen receptor modulators, such as bazedoxifene or lasofoxifene to date. No case of ONJ has been reported with hormone replacement therapy, although estrogen exert a more potent antiresorptive effect than RLX, perhaps because of its limited current use. Notably, 2 cases of ONJ have been reported with romosozumab, a potent agent with both anabolic and antiresorptive effects, in OP patients with confounding factors (141).

In most (88, 121, 122, 128, 142) but not all (119, 124, 143) of the studies and meta-analyses in cancer patients with BM, the incidence of MRONJ was higher in those treated with Dmab than in BP-treated, mostly ZOL-treated, patients. A higher MRONJ incidence with Dmab was recently reported for OP patients as well (144). In the pivotal controlled, double-blind, double-dummy trials of ZOL vs Dmab, a preplanned pooled analysis of the 3 trials (breast, prostate, and other tumors), reported numerically more cases of ONJ after Dmab than after ZOL but the difference was not statistically significant ($P = .13$) (145). Consistently, in BM patients, replacing ZOL with Dmab was a risk factor for developing MRONJ (146-148). However, as reporting below, imaging characteristics of BRONJ and DRONJ may differ (63), potentially affecting the incidence reported for earlier stages, while including different type of cancers, some more prone to ONJ development than others, could modify the meta-analysis results. Importantly, MRONJ caused by Dmab has been reported to occur earlier than with BPs (149, 150) but also resolved faster (88). Of note, Dmab is more efficacious than BPs in preventing and delaying SREs in patients with solid tumors and MM (119, 128, 145).

Finally, the type of BP used may affect the risk of MRONJ development (96). MRONJ incidence is considerably higher with IV BPs compared to oral BPs (151) largely because oral BPs are mostly used for benign diseases whereas IV BPs are used for malignancies, in much higher and more frequently administered doses. In an in vitro study in human fibroblasts and osteoblasts, ALN suppressed cell viability and migration, and induced apoptosis more than IBN and similarly as ZOL (152). ZOL-treated cancer patients had a higher risk of MRONJ than those treated with PAM or sequentially with PAM and ZOL (96), or sequentially with ZOL and IBN (153). Similarly, in breast cancer patients receiving adjuvant BP therapy, MRONJ was higher with ZOL (1.26%) compared with oral CLO (0.36%) and IBN (0.77%) (154). Also in adjuvant breast cancer therapy, MRONJ was reported only with ZOL and not with CLO, PAM, RIS, or IBN (155). In OP patients, MRONJ was significantly more common with ALN than with RIS or PAM (8). Similarly, ALN was accountable for 77% of MRONJ cases attributed to oral BPs in a review of 2400 cases (10). Finally, a recent in vitro study suggested that the risk of MRONJ might be quite lower with nonamino-BPs than with amino-BPs because of their more potent antioxidant and anti-inflammatory effects (156).

## Clinical Presentation and Imaging

### Clinical Presentation

Signs and symptoms of MRONJ may include local pain, mucosal swelling, erythema, tooth mobility, tooth abscess, ulceration (15, 157), altered sensation because of compression of the nerves by surrounding inflammation (158, 159), and even paresthesia or anesthesia of the associated branch of the trigeminal nerve (159). However, exposed bone may remain asymptomatic for a long time and manifest clinical features only when inflammation of the surrounding tissue occurs (160).

Unfortunately, early signs of MRONJ include nonspecific sinus pain, odontalgia, and altered neurosensory function (71), which may prevent diagnosis and require a high index of suspicion when evaluating patients on antiresorptive and/or antiangiogenic agents.

Later findings could be fistulae, developed when necrotic jawbone tissue becomes infected (161), and chronic maxillary sinusitis with or without an oral-antral fistula secondary to maxilla osteonecrosis; the latter may rarely be the presenting feature in these patients (162, 163).

Oral and general quality of life (QoL) is affected in individuals who develop MRONJ (164, 165), and worsens with advancing of ONJ stage (165). The deterioration is mainly attributed to symptoms (mostly pain and chewing difficulties), feeling of uncertainty, speech difficulties, weight loss, and socializing issues (166). Pharmacological management and even more surgical intervention may improve QoL (166, 167).

### Imaging

Imaging is critical both for diagnosis and the assessment of disease progression. The most used modality is panoramic radiography (or orthopantomography or OPG x-ray), which can identify early changes in the jaws, such as thickening of the lamina dura, widening of the periodontal ligament space, increased trabecular density of the alveolar bone, or even sequestration (168). In later stages findings vary, ranging from high bone density, dense woven bone, thickening of the periosteum, opacities, radiolucencies, and osteolysis (169), to diffuse osteosclerosis along with extended osteolysis of the surrounding bone tissue, and even pathologic fracture of the mandible in stage 3 of ONJ (161, 168).

Computed tomography and magnetic resonance imaging are considerably more sensitive than OPG x-ray and, despite their low sensitivity, can aid in diagnosis and provide qualitative assessment, with cone-beam computed tomography being the reference standard (170), and ultrashort echo-time magnetic resonance imaging recently proven equally useful (171). Bone scintigraphy could provide early detection of MRONJ in high-risk individuals (172).

Of note, although BP- and Dmab-induced MRONJ share a similar clinical presentation, their imaging characteristics may be quite different, although no characteristic is exclusively observed in 1 of them but rather the frequency and extent of each characteristic differs among these 2 entities (63, 173).

## Prevention and Management

### Medication-related Osteonecrosis of the Jaw Prevention

To determine the best approach for each individual patient, it is necessary to weigh the risks of MRONJ with the risk of fracture in OP patients and the risk of CTIBL and SREs in cancer patients. The MRONJ risk will be affected by comorbidities as well as the extent of the planned oral surgery.

To preserve oral health, coordination of care between the dentist and the bone specialist or the oncologist is strongly recommended.

#### Osteoporosis patients

Although MRONJ risk is very low in these patients, primary prevention is recommended to restore and maintain good oral health (84). We emphasize the importance of usual oral hygiene. For patients not regularly checked by their dentist, we recommend a dental examination be performed at or shortly after the initiation of antiresorptive treatment. This may include radiologic tests as needed. We recommend that physicians and dentists be well educated in terms of ONJ. Primary prevention should be maintained throughout treatment, risk factors should be minimized, and regular dental follow-up is recommended (Fig. 2A). Any planned oral procedures or surgeries should be performed before or shortly after the antiresorptive treatment initiation (174-177). Appropriate oral health care should be planned with the oral hygienist and/or the dentist. Poorly fitting dentures should be replaced because local oral trauma is a risk factor for ONJ (98, 178, 179). In addition to general preventive measures, the following can be considered when extradental procedures are performed, especially after long-term treatment:

- antimicrobial mouth rinsing (180-182)
- use of antibiotics before and/or after the procedure (175, 181-183). Although there is no consensus, the regimen most widely used in countries with widespread antibiotic resistance includes broad-spectrum antibiotics, such as amoxicillin/clavulanic acid, and clindamycin or metronidazole in combination or even as monotherapy. In contrast, narrow-spectrum antibiotics are preferably used in some of the ECTS membership countries where resistance to antibiotics is low. Consequently, this practice may differ among countries depending on the considerable differences in bacterial resistance across Europe. Furthermore, dosages and duration of therapy vary because of lack of precise guidelines.

#### Cancer patients

Since MRONJ risk is considerably higher in cancer patients than in OP patients, a thorough initial clinical and imaging dental evaluation is recommended, and oral procedures or surgeries should be performed before the initiation of antiresorptives (184) (Fig. 2B). Patients should be strictly educated on maintaining good oral health and on recognizing early ONJ signs and symptoms (see Fig. 2). Simple and low-cost preventive measures include the use of saline or sodium bicarbonate mouthwashes (185-187) and fluoridated toothpastes (188, 189). Frequent communication with patients is encouraged (see Fig. 2A). Attention should be paid to minimize modifiable risk factors such as poorly controlled diabetes (112), smoking (111-113, 190-192), ill-fitting dentures (98, 178, 179, 193), and poor dental and periodontal health (100, 176, 179, 193-198).

Prophylactic antibiotic treatment before dental procedures significantly decreases MRONJ risk (175, 176, 199). Nonurgent dentoalveolar surgery should be avoided during antiresorptive treatment at oncologic doses if possible. Otherwise, it should be planned based on cancer staging, risk assessment, and more appropriate timing.

### Medication-related Osteonecrosis of the Jaw Management

Although several different guidelines have been published in the last 15 years, treatment strategies are based on limited evidence. In general, both in OP and cancer patients, MRONJ treatment depends on the stage of ONJ and the symptoms present and treatment providers should consider several clinical variables that will influence the outcome including the underlying disease, ONJ severity, age, sex, prognosis and life expectancy, comorbidities, symptoms, and estimated bone fragility, to define the optimal therapeutic approach.

#### Conservative management

Conservative treatment is the basis of care of patients with ONJ (200-205) (Fig. 3). In many cases it is the only treatment

needed and achieves long-term symptom relief (94, 206, 207). Cure rates with conservative management are higher for OP than for cancer patients (207). Management includes the following:

- maintenance of optimal oral hygiene, including self and regular professional care;
- treatment of any dental and periodontal disease;
- antiseptic mouth rinses; and

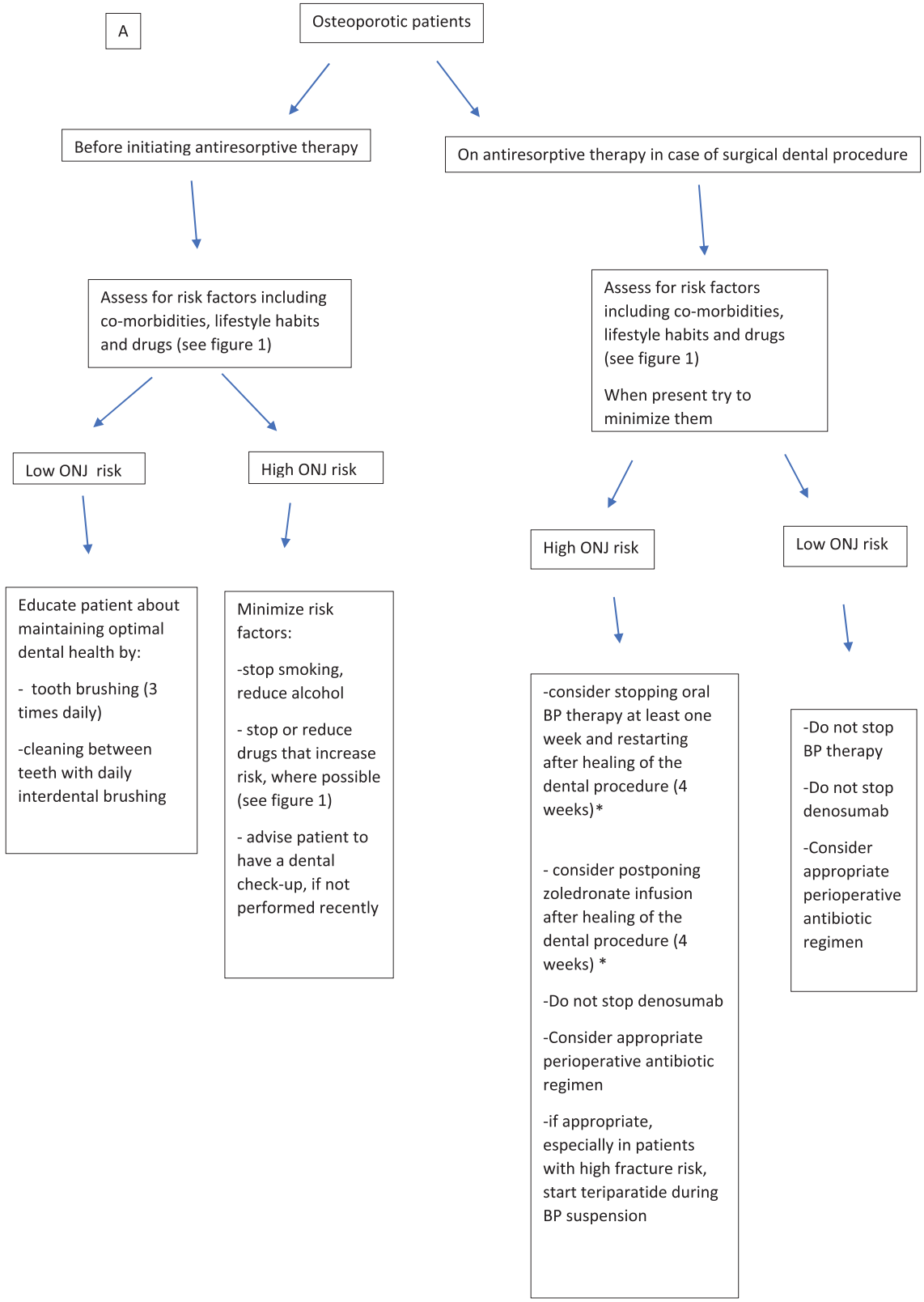


**Figure 2.** Recommendations for prevention of antiresorptive agent-related osteonecrosis of the jaw in patients taking bone-modifying agents (BMA) due to A, osteoporosis, and B, cancer. ONJ, osteonecrosis of the jaw; RCT, randomized controlled trial. *In the absence of RCT.

- systemic antibiotic therapy, if indicated. Dosages and duration of therapy varies depending on the stage of ONJ and the general condition of the patient.

Conservative management is mainly applied in the earlier stages of ONJ (see Fig. 3):

- At-risk patients: Close clinical and radiographic monitoring is advised but there is no need for intervention. Nevertheless, patients must be informed about the possibility of bone exposure and necrosis and be able to early identify signs and symptoms
- Stage 0: Since symptoms are not specific, the objective is to symptomatically control pain and infections, and closely monitor for signs of progression

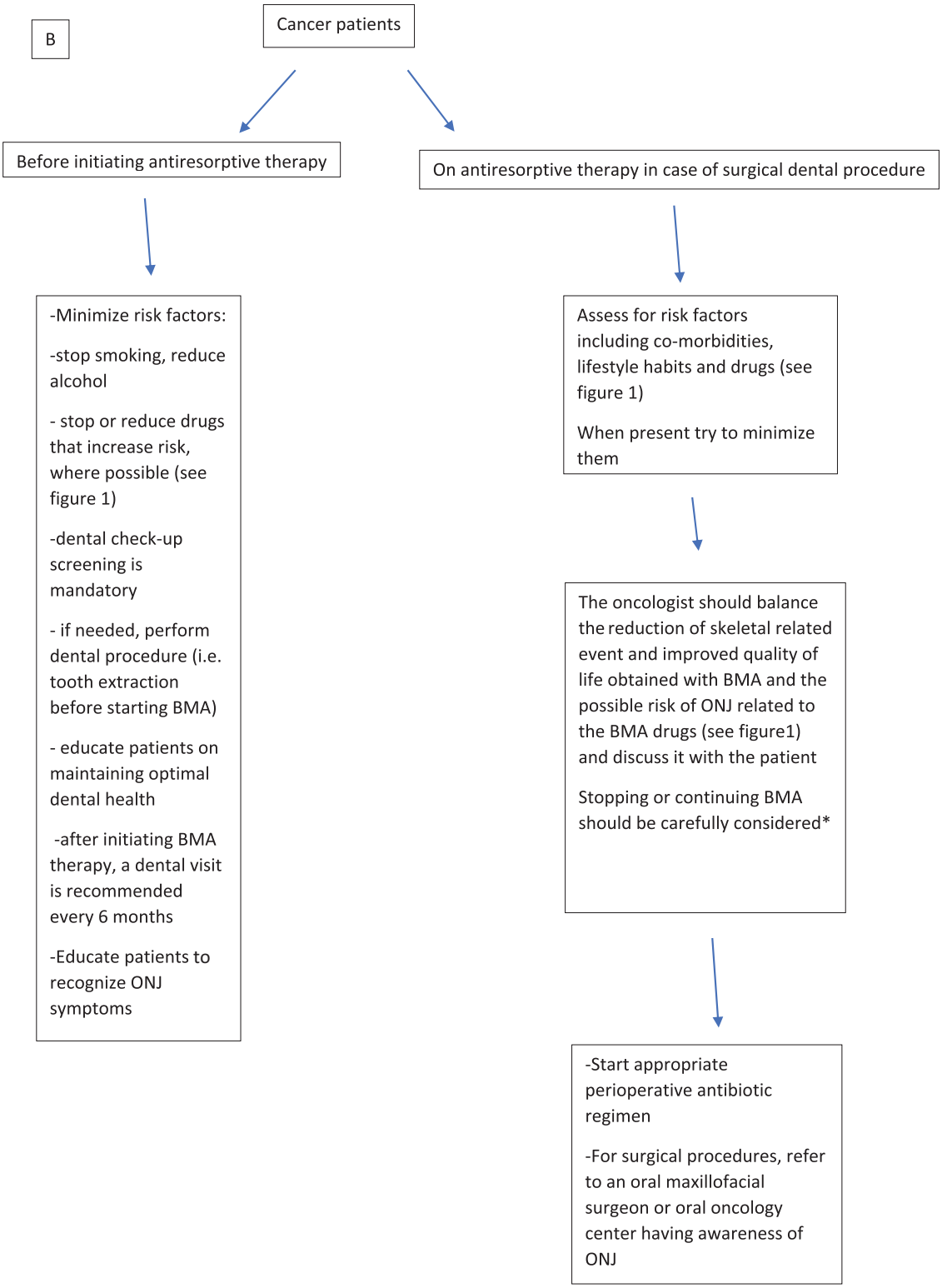


**Figure 2.** Continued.

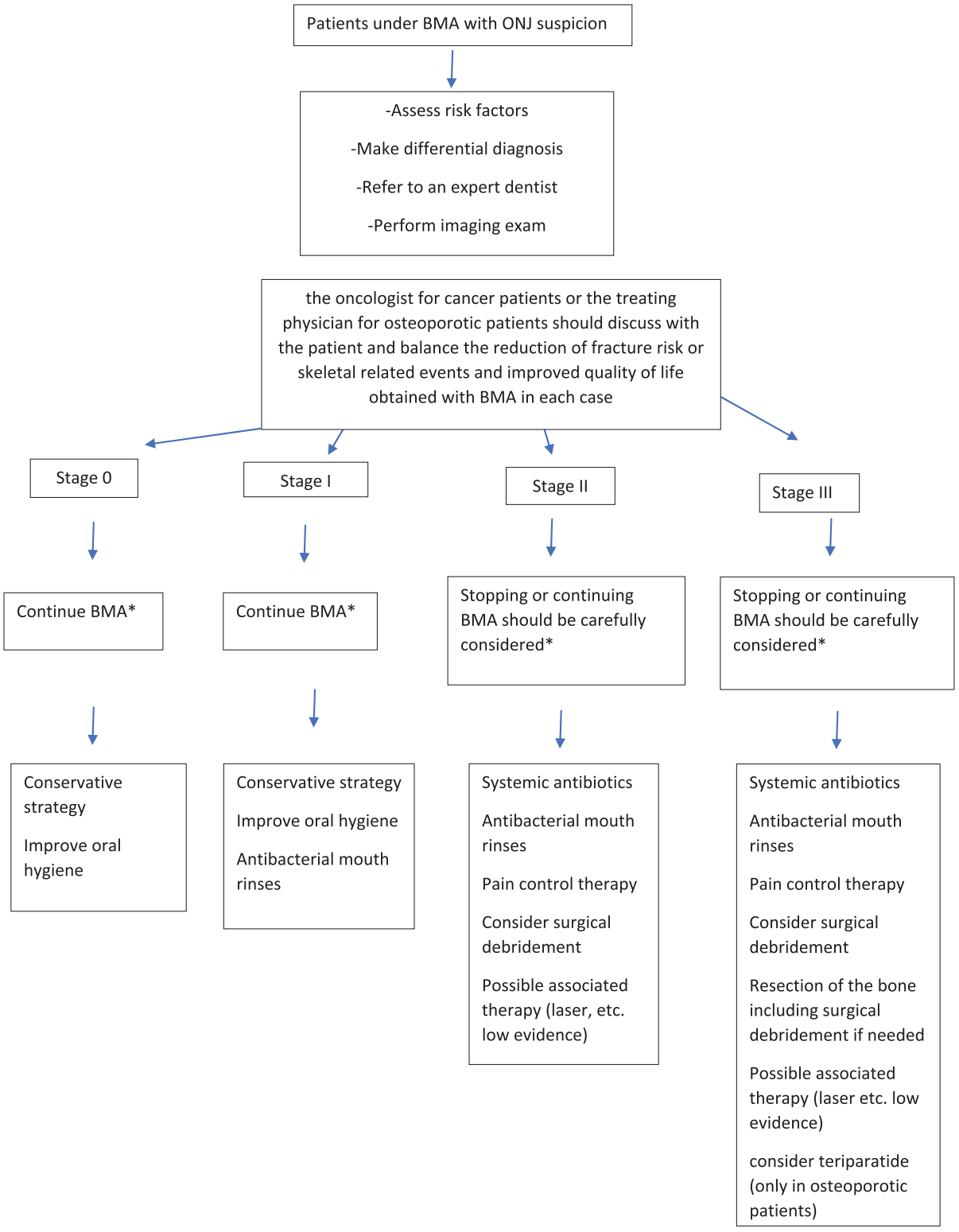


**Figure 3.** Recommendations for management of antiresorptive agent-related osteonecrosis of the jaw in patients taking bone-modifying agents (BMA). Staging of antiresorptive agent-related osteonecrosis of the jaw according to the American Association of Oral and Maxillofacial Surgeons (2014). ONJ, osteonecrosis of the jaw; RCT, randomized controlled trial. *In the absence of RCT.

- Stage 1: Management with chlorhexidine mouthwash and regular follow-up. Neither antibiotic nor surgical intervention is required
- Stage 2: Owing to necrosis and associated infection, an antibiotic regimen with an antimicrobial mouthwash and oral antibiotics is the treatment of choice

Teriparatide (TPTD) was helpful in ONJ management in several case reports (22, 23, 208-215). In a recent study in patients with established MRONJ, TPTD treatment for 8 weeks resulted in a significantly higher number of lesions healed and reduced bone defects by 52 weeks compared with placebo (216). Once-weekly TPTD was also effective (217). At

present, TPTD treatment is contraindicated in patients with active malignancies or a history of BM or skeletal radiation. However, given the rapid turnover of TPTD, a brief exposure (eg, 8 weeks) will most likely not affect the "alleged" risk of osteosarcoma, reported in rats but never demonstrated in humans (218), or activate quiescent malignant cells.

Weak evidence suggests other experimental conservative treatments may be helpful (Table 4).

Conservative therapy should be preferred over surgical management unless obvious progression of disease is observed or the pain is not controlled by conservative means.

**Surgical management**

Surgical treatment should be performed by experienced dentists or surgeons. Surgical management is applied in the latter stages of ONJ (see Fig. 3):

- Stage 2: Besides the antibiotic regimen reported earlier, debridement is often needed (232-238)
- Stage 3: Surgical management is indicated along with an antibiotic regimen. The surgical approach varies (232-238), ranging from limited debridement to complete resection with possible immediate reconstruction with plates or obturators (232, 239). A more conservative treatment should initially be considered, limiting operative therapy for cases not solved by this approach (238, 240, 241). However, the limited available data do not allow conclusive indications on surgical intervention. According to previous guidelines, removal of the necrotic bone with tension-free closure should be preferred, as it is considered to provide the most positive results.

Surgical success rates have been reported higher in OP and MM patients in comparison to patients with solid tumors (242).

Adjuvant treatments have also been proposed (243), although scientific evidence has often been controversial because of the lack of randomized controlled trials (Table 4).

## Special Considerations

Table 5 presents the suggested approaches in i) dental procedures in low- and high-risk patients receiving antiresorptive treatment, and ii) patients receiving antiresorptives who develop ONJ.

A balanced evaluation of the risk-to-benefit ratio of continuing or stopping antiresorptives should always be performed in such patients. A detailed medical history should be obtained, evaluating the duration and type of antiresorptives (current or past), concurrent pharmacological treatments, the presence of other risk factors for ONJ, and the risk of fracture or SRE. Clinical decision should also be made in relation to the invasiveness of the procedure.

Discontinuation of antiresorptive treatment in patients requiring dental procedures is particularly controversial because of low evidence to support strong recommendations. The following are the most accepted guidelines:

- American Dental Association Guidelines in 2011 recognized the lower risk in OP patients and stated that discontinuation of oral BPs is not necessary before dental procedures (200)
- The AAOMS, admitting the lack of scientific evidence, suggested in 2014 a drug holiday in patients who have been on BPs or Dmab for at least 4 years (6)
- The US Food and Drug Administration stated there are "no substantial data available to guide decisions regarding the initiation or duration of a drug holiday" (258)
- An ONJ International Task Force in 2015 recommended stopping antiresorptive treatment in patients needing extensive invasive surgery or presenting with significant ONJ risk factors (64) until soft-tissue healing has occurred.

Our recommendations on the subject, along with our concerns, are summarized in Table 5. Discontinuation until the surgical site heals could be considered in case of BPs, especially if the fracture risk is low and the MRONJ risk is high. Theoretically, since the uptake of BPs is comparatively increased at sites of local bone injury with high bone turnover, withholding BP treatment may reduce their local deposition in the jawbone. It has been proposed that BPs may be discontinued 1 week before the procedure and resumed when healing of oral mucosa is completed (84, 245), usually 2 to 4 weeks after the dental treatment (9, 74). However, the optimal duration of the off-treatment period is unknown and, furthermore, the efficacy of such an approach is questionable given the residual effect of BPs due to their long-term skeletal retention and the fact that no study results to date have confirmed that drug holidays are effective in preventing MRONJ. Recent evidence from a study in OP patients (249) suggests that tooth extraction can be safely performed without BP discontinuation while suspension of BP treatment in animals (250) and humans (251, 252) who developed MRONJ did not provide any significant benefit. Lower doses of antiresorptive therapy have also been proposed (74), but without supporting evidence. Especially in cancer patients, in whom the vast majority of MRONJ incidents occur, although it has been recommended to withhold

**Table 4.** Adjuvant therapies applied in management of osteonecrosis of the jaw

| During conservative management | During surgical management |
|---|---|
| • Bone marrow stem cell intralesional transplantation (219) | • Laser-assisted surgical debridement (220, 221) |
| • Leukocyte and platelet rich fibrin membrane placement (183, 222, 223) | • Preoperative antibiotic treatment followed by laser and wound local treatment with platelet-rich plasma applications (224) |
| • Ozone (225) | • Surgical debridement in combination with platelet-derived growth factor (183) |
| • Pentoxifylline (226) | • Intraoperative fluorescence guidance (227, 228) |
| • Vitamin E (226) | • Longer-term preoperative antibiotics (229) |
| • Hyperbaric oxygen therapy | • Adjunctive therapy with hyperbaric oxygen combined with surgery (230, 231) |

**Table 5.** Recommendations for dental management in specific conditions

| |
|---|
| **A.Dental procedures during antiresorptive therapy** |
| **Patients at low risk of ONJ** |
| Conservative treatments (restorative treatment, non-surgical endodontic treatment, prosthodontic/orthodontic therapy) are safe[a] |
| Elective dentoalveolar surgery, simple extractions, and procedures that do not involve osteotomy are considered to be of low risk (9) |
| Placement of dental implants entails small risk |
| Antimicrobial mouthwash before/after procedure is advised. Systemic antibiotics are also advised in nonconservative treatments (180) |
| ***Antiresorptive treatment management*** |
| **Osteoporotic patients** |
| Do not discontinue bisphosphonates[b] |
| Do not discontinue denosumab—perform procedure preferably 5-6 mo following the last injection |
| Lower doses of antiresorptives (74)? No supporting evidence |
| **Cancer patients** |
| Do not discontinue bisphosphonates[b,c] |
| Do not discontinue denosumab |
| ***Patients at high risk of ONJ*** |
| Mild conservative treatments (restorative treatment, removal of dental caries) are usually safe |
| Nonsurgical endodontic treatment has a small risk—could be an alternative to extraction (244)[d] |
| Root canal treatment and/or decoronation preferred over extraction (244) |
| Antimicrobial mouthwash, systemic antibiotics before/after the procedure, avoidance of anesthetic agents that contain vasoconstrictor, avoidance of gingival tissue damage |
| Denture wearing not prohibited (avoid exerting excessive pressure or friction) (79) |
| ***Antiresorptive treatment management*** |
| **Osteoporotic patients** |
| Bisphosphonates could be discontinued (at least 1 wk before and until surgical site healing) (84, 245)[e] |
| Do not discontinue denosumab—perform procedure preferably 5-6 months following last injection (245, 246)[f]—perform next denosumab injection 4-6 wk after the procedure but not > 4 wk later than it should be done |
| Consider replacing antiresorptives with teriparatide[g] |
| No data on romosozumab |
| **Cancer patients** |
| Personalized decision in agreement with treating oncologist, weighing risk of ONJ against risks of SREs |
| Bisphosphonates could be discontinued |
| Short-term denosumab discontinuation (eg, 3 wk before and 4-6 wk after dental procedure has been advised) (247)—no clear benefit[b] |
| **B.Antiresorptive treatment management in patients who develop ONJ** |
| Consider discontinuing antiresorptives until complete soft-tissue closure after carefully weighing risk of ongoing ONJ with risk of fractures or SREs[i] |
| Consider teriparatide until complete soft-tissue closure (22) (in osteoporotic but probably not in cancer patients—individualized approach)[j] |

Abbreviations: ONJ, osteonecrosis of the jaw; SRE, skeletal-related event.
[a]A few, not well-documented cases of ONJ reported after nonsurgical endodontic procedures (248).
[b]Residual effect of bisphosphonates questions the effect of discontinuation on ONJ; in osteoporotic patients tooth extraction safely performed without bisphosphonate discontinuation (249); suspension of bisphosphonates not beneficial in animals (250) and humans (251, 252) who developed ONJ.
[c]Reduction in SRE risk is greater and the risk of ONJ lower in first years of bisphosphonate therapy (247).
[d]Soft-tissue damage during endodontic treatment has also been associated with initiation of ONJ process (253).
[e]Unknown optimal duration of off-treatment period.
[f]Based on denosumab pharmacokinetics, its effect on bone turnover is almost depleted around 6 months following the last injection (245, 246).
[g]Concerns: limited duration of teriparatide treatment (23); temporary decrease at least of hip bone mineral density (254); uncertain effect on rebound phenomenon after denosumab discontinuation (246).
[h]OPG-Fc discontinuation before tooth extraction ameliorated subsequent ONJ development in rodents (250); in contrast, in a multicenter retrospective Japanese study short-term denosumab discontinuation had no effect on ONJ risk (255).
[i]Concerns: denosumab discontinuation infers increased risk of multiple vertebral fractures (256, 257); discontinuation of either ZOL or OPG-Fc in rats with established ONJ did not lead to ONJ resolution (250).
[j]Teriparatide is theoretically contraindicated in cancer patients but a brief exposure (eg, 8 wk) should not activate quiescent malignant cells.

antiresorptive therapy following dental procedures until soft-tissue healing has occurred (64), current evidence supporting this recommendation is limited and controversial, with some studies showing a benefit (242, 259) while others have shown a neutral effect on the outcome of the dental procedure (94, 260, 261).

In Dmab-treated OP patients, discontinuation should be discouraged in light of the risk for multiple vertebral fractures (256, 257, 262). Instead, based on the pharmacokinetics of Dmab, dental procedures could be planned at around 5 to 6 months following the last injection, when the effects of Dmab on bone turnover are depleted (245, 246). In cancer patients, Dmab could be withheld but only for a short period (3 wk before to 4-6 wk after the dental procedure) (247), because of the risk both of multiple vertebral fractures and SREs. However, there is no evidence that such a strategy

reduces MRONJ risk and bone turnover will probably remain suppressed during this interval. In animals, discontinuation of OPG-Fc, a molecule resembling Dmab in action, before tooth extraction ameliorated subsequent ONJ development (250). On the contrary, in a multicenter retrospective Japanese study in cancer patients receiving oncologic doses of Dmab, short-term Dmab discontinuation had no effect on the risk of MRONJ (255).

## Conclusions

Preventive measures, including maintenance of good oral health, completion of any required dental treatment before commencing antiresorptive therapy, at least in patients with metastatic bone disease, and use of antibiotics before and after a surgical procedure substantially reduce the risk of MRONJ. Conservative treatment is the mainstay of treatment and should be applied to the majority of MRONJ cases. Surgery remains the main treatment in nonresponsive cases of MRONJ. TPTD is a potential promising conservative therapeutic option in OP patients. However, this and other therapeutical approaches that have been proposed need further validation. Barriers to treatment, health care disparities, and underestimation of bone fragility by most health care providers should be considered.

The benefits of antiresorptive therapy far outweigh the potential risks, with major reductions in SREs in the oncology patient and fracture risk reduction in the OP patient, but ONJ can also severely affect QoL; therefore a personalized treatment plan with careful consideration of all aspects is of the utmost importance.

## Acknowledgments

We would like to thank B. Abrahamsen, P. Hermann, and B. Langdahl for their valuable contribution to the finalization of the manuscript.

## Financial Support

The authors received no financial support for the research, authorship, and/or publication of this article.

## Author Contributions

Literature research, data collection, and drafting of the first version of the manuscript: A.D.A., J.P., and N.N.; revising manuscript content: A.P., C.M., K.A.A., M.C.Z., and J.J.B.; approval of the final version of the manuscript: A.D.A., J.P., N.N., A.P., C.M., K.A.A., M.C.Z., and J.J.B.

## Disclosures

A.D.A. has received lecture fees from Amgen, Eli Lilly, UCB, and VIANEX. J.P. has nothing to disclose. N.N. has received consultant fees from UCB, a speaker fee from Eli Lilly, and research support from Abiogen. A.P. has received honoraria for lectures from Amgen. C.M. has nothing to disclose. A.K. has received research funds received from Alexion, Amgen, Ascendis, Chugai, Radius, Takeda, and Ultragenyx. M.C.Z. has received honoraria for lectures or advice from Alexion, Amgen, Eli Lilly, Kyowa Kirin, Shire, and UCB. J.J.B. has received consulting fees from Cole Pharma, Sandoz, Takeda, and UCB.

## Data Availability

Data sharing is not applicable to this article because no data sets were generated or analyzed during the present study.

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