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General and Supportive Care

Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases

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ABSTRACT

Medication-related osteonecrosis of the jaw (MRONJ) is primarily an adverse side effect of denosumab or bisphosphonates (particularly when used at high doses to prevent skeletal-related events [SREs] in patients with cancer and bone metastases) or possibly anti-angiogenic cancer treatment. While the implementation of preventive measures over recent years has reduced the risk of MRONJ in patients with bone metastases due to cancer, it is imperative to balance the risk of MRONJ against the beneficial effects of treatment with denosumab or bisphosphonates on the skeletal health of patients. Despite growing awareness of MRONJ within the medical community, there is a lack of large-scale, prospective clinical studies in this rapidly evolving field. Discussing preventive measures with patients and implementing them, both before and during treatment with bisphosphonates or denosumab, is the best option to reduce the risk of MRONJ. In particular, avoiding bone trauma and preventing and treating dental infections before and during denosumab or bisphosphonate therapy is crucial to minimize the risk of MRONJ. If MRONJ develops, conservative (non-surgical) treatment can provide symptom relief, but achieving mucosal closure remains challenging. When management of symptoms and mucosal healing are the ultimate goals of therapy, or after failure of conservative treatment, a surgical approach may be beneficial. This critical review, based on a best-evidence review of currently available literature, provides clear practical guidelines to help to prevent, manage and treat MRONJ. Overall, a multidisciplinary, pragmatic approach to MRONJ should be adopted, prioritizing patient's quality of life and management of their skeletal malignant disease.

Introduction

Patients with cancer that has metastasized to bone and individuals with osteoporosis are at risk of developing skeletal complications, including fractures, which can lead to pain, decreased quality of life (QoL) and lengthy stays in hospital [1–5]. High-dose regimens of bisphosphonates (such as zoledronic acid 4 mg every 3–4 weeks intravenously [5]) and the monoclonal antibody denosumab (an agent that targets receptor activator of nuclear factor kappa B ligand [RANKL]; 120 mg every 4 weeks subcutaneously [SC]) are approved for the prevention of skeletal-related events (SREs) in adults with advanced malignancies involving bone; low-dose regimens (such as zoledronic acid 5 mg yearly IV; denosumab 60 mg every 6 months SC) are approved for the treatment of osteoporosis [6–9]. Zoledronic acid (4 mg every 3–4 weeks) can also be used in patients with bone lesions associated with haematological malignancies and denosumab (120 mg every 4 weeks) has been approved in the USA for prevention of SREs in patients with multiple myeloma (MM) (European approval is pending) [6,10]. In a phase 3 trial, denosumab demonstrated non-inferiority to zoledronic acid in time to first SRE in patients with newly diagnosed MM. Overall survival was similar between the groups; however, an exploratory analysis showed that denosumab was associated with a 10.7 month progression-free survival benefit compared with zoledronic acid [11]. Treatment with high-dose denosumab or zoledronic acid has been shown to delay the time to onset of SREs, lower the risk of subsequent SREs and reduce pain in patients with cancer and bone metastases; denosumab has also been shown to maintain QoL for longer than zoledronic acid [12,13]. In addition, high-dose denosumab is

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indicated for the treatment of skeletally mature patients with giant cell tumor of bone (GCTB) that is unresectable, or if surgical resection is likely to result in severe morbidity [7].

Osteonecrosis of the jaw (ONJ) is an adverse side effect of treatment with denosumab or bisphosphonates [14]. The risk of medication-related ONJ (MRONJ) is dependent on treatment exposure, and more than 90% of MRONJ cases occur in patients with cancer and bone metastases who are receiving these agents at high doses for the prevention of SREs [14–16]. MRONJ has also been reported in patients receiving anti-angiogenic drugs and tyrosine kinase inhibitors (such as bevacizumab and sunitinib), but robust incidence data are lacking [17–23].

It is imperative to balance the risk of MRONJ against the benefit of treatment with denosumab or bisphosphonates in patients with cancer and bone metastases, particularly when long-term use may be indicated [14]. This is not straightforward. For example, there is a lack of clear data on the value of pausing treatment with denosumab or bisphosphonates to manage the risk of MRONJ [14], whilst the development of MRONJ may restrict their use and delay chemotherapy in cases of advanced MRONJ [24]. There is a need for improved awareness and understanding of MRONJ among some healthcare professionals (HCPs); general dental practitioners, for example, may lack full understanding of the treatments used for the underlying malignancy [25].

More research is required into many aspects of MRONJ, such as the pathogenesis and risk factors – including the role of dental infections and extractions – and the best approaches to prevention, diagnosis and management [26]. In light of this evolving research landscape, it remains important for HCPs to understand the current best practice for reducing the risk of patients developing MRONJ [14,27] and optimizing skeletal outcomes for individuals who have proven MRONJ. This is pertinent as the incidence of MRONJ will probably increase with improved survival of cancer patients [28]. Furthermore, cancer treatments increasingly target multiple biological pathways (including angiogenesis) [29], which, in theory, may also contribute to an increased risk of MRONJ.

Efforts to prevent, diagnose and manage MRONJ require a multidisciplinary approach involving oncologists, dentists and maxillofacial surgeons. This review focuses on the clinical strategies that may be used for this purpose, particularly in patients with cancer that has metastasized to bone.

Medication-related osteonecrosis of the jaw: an overview

Diagnosis and staging

According to a position paper published by the American Association of Oral and Maxillofacial Surgeons (AAOMS) in 2014, MRONJ is defined by presence of all of the following: current or previous treatment with bisphosphonates or denosumab or anti-angiogenic therapy; an area of exposed jawbone or bone that can be probed through at least one intraoral or extra oral fistula that has persisted for more than 8 weeks; and no history of radiation therapy to the jaw or obvious metastatic disease of the jaw [14]. The most widely used staging system for MRONJ is that described by the AAOMS; this reflects disease presentation and can assist in the appropriate stratification of patients (Figs. 1–3) [14]. In addition to the stages requiring specific management approaches, as shown in Fig. 1, an initial stage 0 is described, in which there is no clinical evidence of necrotic bone, and yet patients present with non-specific symptoms or clinical and radiographic findings [14]. The treatment strategy in such cases is systemic (e.g. pain medication and, if appropriate, antibiotics) [14].

It is important that physicians remain vigilant for MRONJ and are aware of the key signs and symptoms, which include the following: pain; exposed necrotic bone; signs of infection such as fistula(e), swelling, cellulitis and pus exudation; hypoesthesia or paraesthesia in the lower lip or chin region; loosening of teeth; and halitosis [15,19]. Differential diagnosis may be challenging; periapical infection and periodontitis can simulate stage 0 MRONJ or higher stages of the condition if a fistula is present [14,27]. Less frequently, gingivitis, alveolar osteitis, chronic sclerosing osteomyelitis, osteoradionecrosis, fibro-osseous lesions and temporomandibular joint disorders may also be mistaken for MRONJ [14,27].

The stage of MRONJ at presentation is prognostic for the success of conservative (non-surgical) treatment, with only a very low likelihood of healing in patients who have higher stages of the disease [30–32]. In these patients, or after failure of a conservative treatment trial, a surgical approach offers the best chances of healing [30,33]. However, controversy exists regarding the staging of MRONJ. Some physicians have questioned the clinical relevance of prodromal stage 0 – during which there is no clinical evidence of necrotic bone – because the lack of specificity of the current criteria makes it difficult to assess whether stage 0 cases will progress to later stages of MRONJ [34]. Conversely, ignoring early signs and symptoms may delay diagnosis and potentially reduce the chance of curative intervention [35].

Clarity is also required within guidelines regarding the diagnosis of non-exposed MRONJ – where patients have no clinical evidence of necrotic bone, but present with nonspecific symptoms or clinical and radiographic findings [36] – which was not included in the 2015 guidelines issued by the International Task Force on ONJ [27]. For example, infection and involvement of the maxillary sinus without bone exposure or fistula could be classified as stage 0 because of the lack of exposed bone, stage 2 because of signs of infection, or even stage 3 owing to involvement of the maxillary sinus. This ambiguity emphasizes the need for a more precise definition of non-exposed-MRONJ that has been validated and globally accepted.

While ONJ is typically diagnosed clinically, the use of orthopantomography is required to provide an initial estimate of the extent of disease. In addition, the use of more advanced imaging modalities (such magnetic resonance imaging, or alternatively cone beam computed tomography or computed tomography) is advised, particularly when surgical intervention is considered.

Another challenge that should be considered by HCPs when staging MRONJ is the lack of size criteria in the current staging system, meaning that disease affecting an entire quadrant can be staged identically to a lesion less than 1 cm in diameter, even though the likelihood of favorable outcome may be totally different.

Risk factors

In addition to recognizing the signs and symptoms of MRONJ, HCPs need to be aware of the risk factors that may contribute to the development and severity of the condition, although the available data are inconclusive.

Exposure to denosumab or bisphosphonates is the primary risk factor for MRONJ; although it has been established that MRONJ can arise following the use of other cancer therapies (e.g. inhibitors of angiogenesis, tyrosine kinase inhibitors). MRONJ following exposure to denosumab and bisphosphonates is the most comprehensively documented in the literature [6,7,22–24]. The risk of developing MRONJ with these treatments increases with more frequent administration, a higher dose per administration (e.g. doses used in the metastatic setting versus in the osteoporosis setting) and a longer duration of treatment [23,37–39]. Data do not support any difference between denosumab and bisphosphonates in time to onset of MRONJ if cumulative exposure and potency are accounted for [19].

The development of MRONJ generally follows a local infection or trauma to the bone (usually surgical trauma or pressure sores) or soft tissue. Typical events that might precede MRONJ include significant periodontal inflammation, pressure sores from ill-fitting prostheses and invasive procedures (e.g. tooth extraction) and other dento-alveolar surgery [23,26,40]. In one study, signs of peri-implantitis were found in 93% of patients (14/15) with peri-implant MRONJ and this may

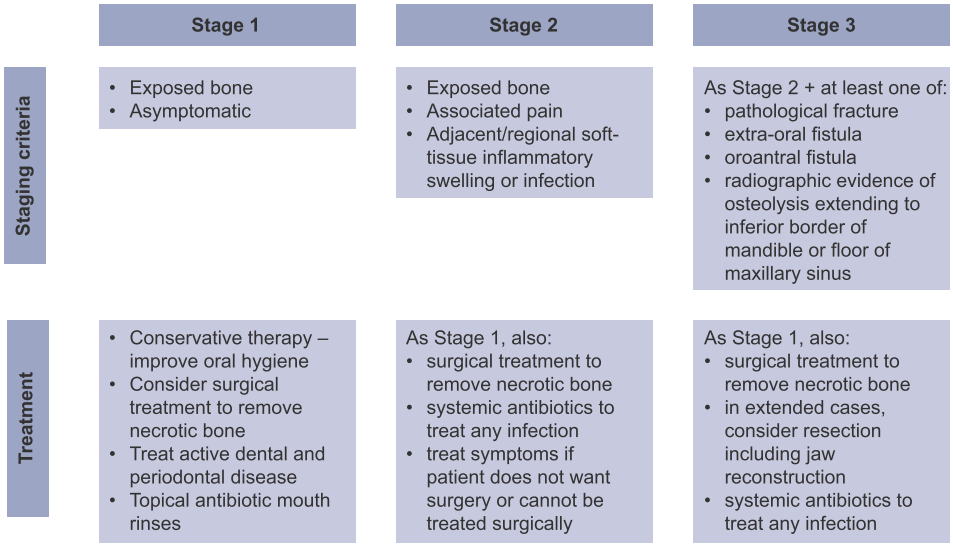

Fig. 1. Key recommendations for staging and treatment of medication-related osteonecrosis of the jaw (MRONJ) [63]. MRONJ, medication-related osteonecrosis of the jaw.

contribute to the aetiology of the condition; nearly all implants (95%) had been placed before patients commenced antiresorptive treatment [40]. Of note, approximately one-third of MRONJ cases occur spontaneously without any identifiable initiating event; in these cases, subclinical trauma is a likely cause [23]. Clinical observation has shown an association between the occurrence of MRONJ and dental extractions and infection, although the underlying mechanism of how these events lead to osteonecrosis remain poorly understood and more high-quality evidence is required [23,26,41,42].

Many additional factors have been reported in the literature as being associated with accelerated development and/or increased severity of the condition, but for most of these it remains unclear whether or not they are causative factors [6,7,15,17–19,24,27,43]. They include the use of corticosteroids, the presence of concomitant diseases or conditions (e.g. pre-existing dental infections, anemia, diabetes-mellitus and immunosuppression or renal failure), poor oral hygiene and smoking [6,7,15,17,19,24,27]. The role of genetic factors in MRONJ is also being investigated in order to help to identify patients at increased risk of MRONJ; however, a robust association between MRONJ risk and a specific genetic variant has not yet been identified [44]. In general, further research is required to elucidate the role of different potential risk factors in the development of MRONJ.

Pathogenesis

The pathogenesis of MRONJ has not yet been fully elucidated and remains an active area of research. It is probably multifactorial, with important roles for infection and trauma to the bone or soft tissue; speculative views on this are considered later.

Inhibition of normal osteoclast function appears pivotal in the pathogenesis of MRONJ, resulting in a reduction of bone re-modeling that hampers the physiological repair and adaptation mechanisms of the jaw bone [45]. In particular, adequate bone re-modeling capacity is thought to be critical in the defence against infection and accumulating microfractures [46–48].

In addition, inhibition of angiogenesis has been observed with zoledronic acid and may contribute to the pathogenesis of MRONJ because reduced blood vessel formation can impair post-interventional healing [17,21,49–51]. MRONJ has also been reported in patients with cancer receiving other agents with anti-angiogenic effects, such as bevacizumab and sunitinib [17,21,51,52].

Preclinical data also suggest that bisphosphonates may exert a toxic effect directly on the oral mucosa, which may also contribute to MRONJ pathogenesis [50,53]. However, it is unknown whether these effects are achieved in clinical practice.

Incidence of medication-related osteonecrosis of the jaw with bisphosphonates and denosumab

High-dose regimens of bisphosphonates or denosumab are associated with an increased risk of MRONJ compared with low-doses regimens [23]. Doses of zoledronic acid or denosumab are higher for patients with bone metastases (4 mg every 3–4 weeks and 120 mg every 4 weeks, respectively) than for individuals with osteoporosis (5 mg once a year and 60 mg every 6 months, respectively) [6–9]. The risk of MRONJ during high-dose treatment was evaluated in an integrated analysis of data from phase 3 studies of 5723 patients with bone metastases associated with solid tumors or MM [19]. The incidence of confirmed MRONJ was 1.8% with denosumab and 1.3% with zoledronic acid ($p = 0.13$), during median exposure of 13.0 and 11.0 doses (at 4-week intervals), respectively [19]. Similarly, the cumulative incidence of MRONJ in patients receiving denosumab for GCTB was approximately 1% after a median time on study of 10.4 months [54]. At the completion of the double-blind part of a phase 3 trial (120 mg every 4 weeks) in patients newly diagnosed with MM, the patient–year adjusted incidence of confirmed MRONJ in the denosumab group (n = 850, median exposure: 19.4 months) was 2.0% during the first year of treatment, 5.0% in the second year and 4.5% per year thereafter [10,11]. When considering low-dose treatment, no cases of MRONJ were reported during the Adjuvant Denosumab in Breast Cancer (ABCSG-18) trial, in which postmenopausal women with early hormone-receptor-positive breast cancer were treated with low-dose (60 mg) denosumab (median follow-up, 94.4 months) [55], and similar data exist for zoledronic acid [56]. Thirteen cases of MRONJ were reported in a phase 3 extension study of 4550 postmenopausal women with osteoporosis receiving treatment with low-dose denosumab for up to 10 years (0.3%; < 0.1 events per 100 patient-years) [9,57]. The risk of MRONJ in a study of 7736 postmenopausal women with osteoporosis receiving low-dose zoledronic acid over 3 years was 0.017% (1.7 cases per 10,000 subjects) [8,58]. No further cases were reported during an extension of this study of up to 6 years [58].

Consistent with the effect of dose and schedule, studies of patients with cancer have established that the incidence of MRONJ increases with the length of exposure to denosumab or bisphosphonate treatment

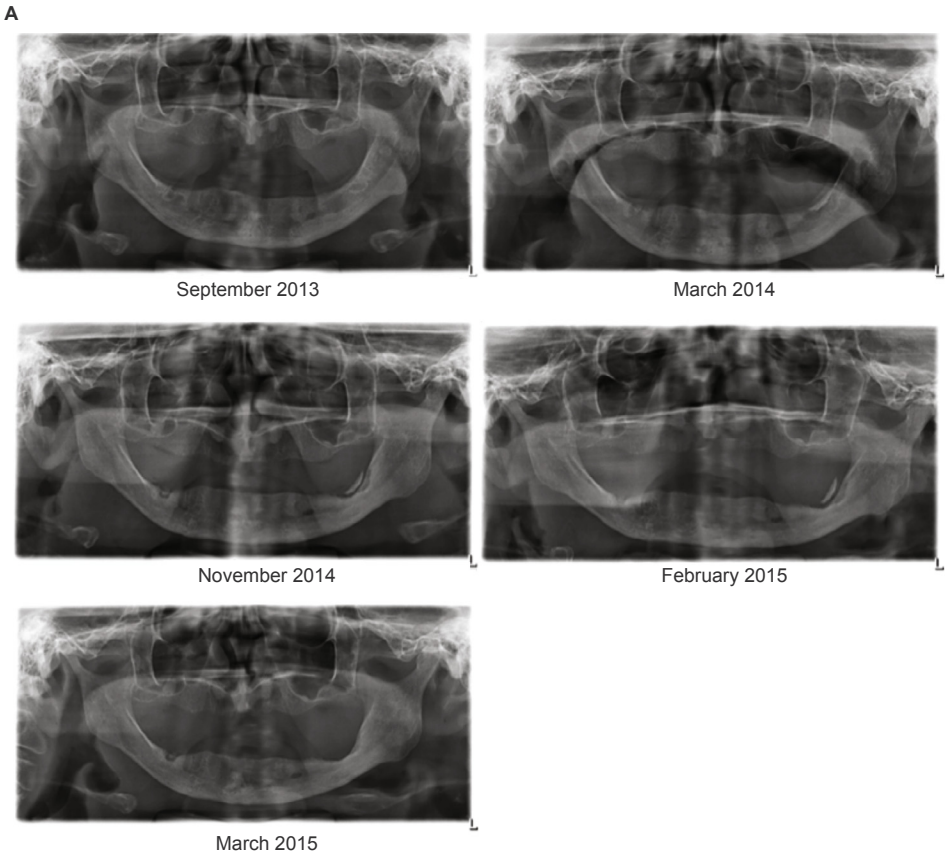

Fig. 2. Clinical and radiological images showing the development of stage 0 medication-related osteonecrosis of the jaw (MRONJ) over time after cessation of denosumab in a patient with breast cancer. Woman aged 66 years with breast cancer who developed severe pain in her left mandible without bone exposure, in the area of a pressure sore, after receiving denosumab for suspected bone metastases. After multidisciplinary discussion, denosumab therapy was stopped because the diagnosis of bone metastases could not be confirmed. No antibiotic treatment was prescribed. (A) The patient reported no additional problems in her jaw, but the bone was gradually sequestered over time most probably due to improvement of bone turnover. (B) Finally, the patient presented with a piece of spontaneously sequestered bone and the soft tissue had almost re-closed. MRONJ, medication-related osteonecrosis of the jaw.

[19,38,39,59]. A prospective study of 252 patients treated with bisphosphonates for bone metastases identified length of exposure as the most important risk factor for MRONJ; the incidence was 1.5% in patients treated for 4–12 months compared with 7.7% for those treated for 37–48 months [60]. In an open-label extension phase of up to 2 years of two phase 3 studies of individuals with metastatic breast or prostate cancer, patients continued to receive denosumab (breast cancer: n = 318; prostate cancer: n = 147) or switched to denosumab from zoledronic acid (breast cancer: n = 334; prostate cancer: n = 118) [38]. For patients who received continuous denosumab during the blinded treatment phase plus the open-label extension phase, the incidence of confirmed MRONJ adjusted for years of patient follow-up was 1.1% during the first year of denosumab treatment, 3.7% in the second year and 4.6% per year thereafter [7,38,39]. The median cumulative exposure to denosumab for these patients was 43.0 months for those with breast cancer (n = 318) and 36.9 months for those with prostate cancer (n = 147) [39].

The risk of MRONJ is an important consideration for HCPs in the management of patients with bisphosphonates or denosumab. In a survey of oncologists and urologists treating men with bone metastases related to prostate cancer in six European countries, 9% of physicians delayed treatment with bisphosphonates or denosumab because of the perceived risk of MRONJ [61]. In a similar survey of oncologists treating women with breast cancer and bone metastases, the corresponding proportion was 8% [3]. Evidence suggests that, in practice, physicians may have a tendency to deviate from registered treatment regimens when agents such as zoledronic acid are used in the long term, in an effort to reduce cumulative exposure [62].

Patients with advanced malignancies who are at risk of developing SREs are likely to experience increased overall survival times as a result of general improvements in cancer care; hence their potential duration of exposure to bisphosphonates or denosumab is also likely to rise. More data are required in order to understand better the most effective prevention and management strategies for MRONJ.

Prevention, management and treatment of medication-related osteonecrosis of the jaw in patients with cancer and bone metastases

MRONJ can be managed effectively with respect to symptom control and QoL, and the risk of developing the condition can be substantially reduced if preventive measures are taken. To achieve the best

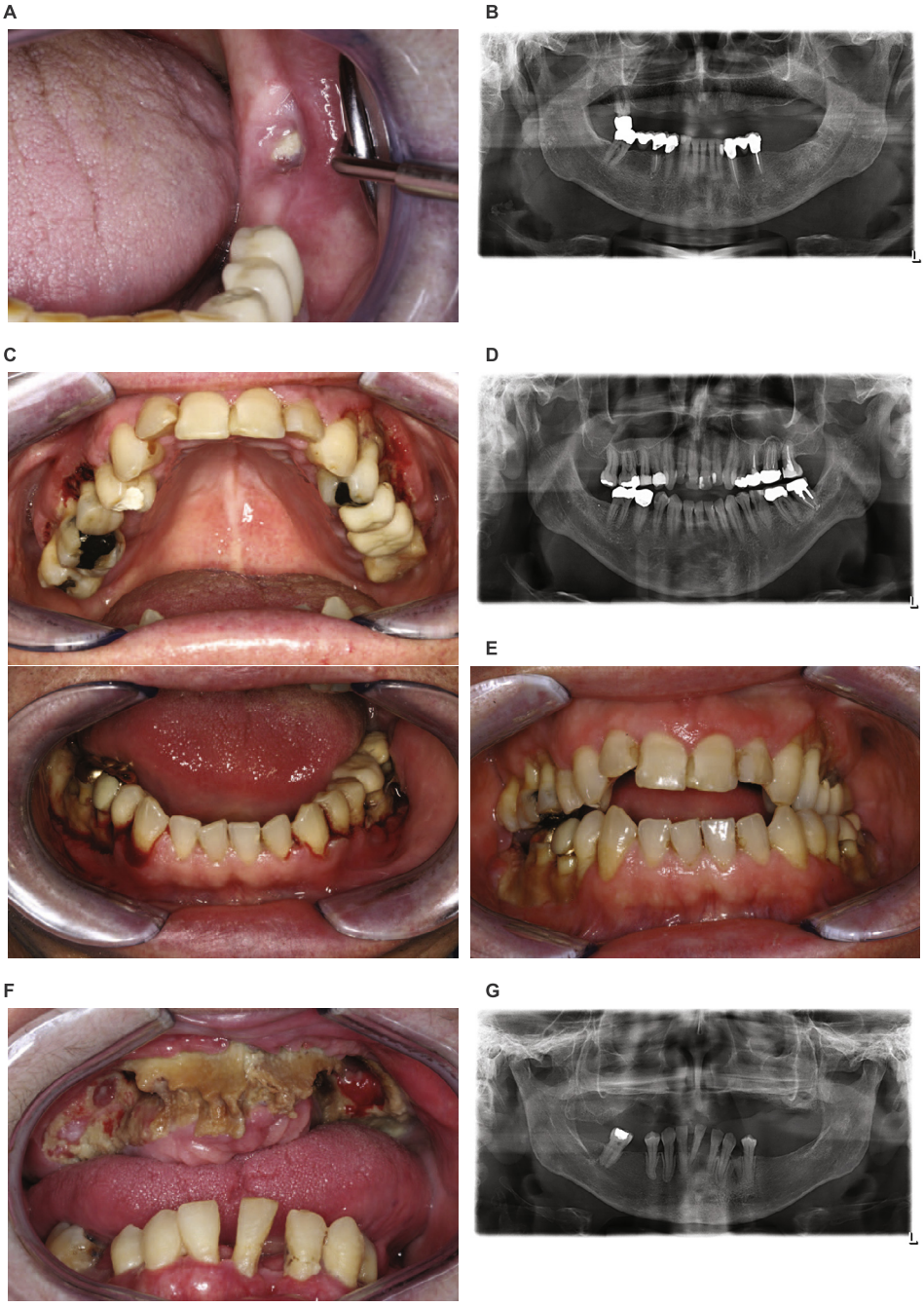

Fig. 3. Clinical and radiological images showing examples of MRONJ of the jaw stages 1–3. Stage 1: man aged 78 years with multiple myeloma who had received pamidronate 90 mg IV every 4 weeks for 2 years. (A) Intraorally exposed necrotic bone was present in region 38 of his left mandible with no signs of infection; the patient was not experiencing any pain. The lesion corresponds to stage 1 MRONJ according to AAOMS 2014 criteria. (B) Panoramic radiograph of the patient showing a persisting alveolar socket in region 38, with surrounding sclerotic changes. Persisting alveolar sockets can also be detected in the maxillary incisor area. Stage 2: man aged 59 years with multiple myeloma who had received zoledronic acid 4 mg IV every 3–4 weeks for more than 2 years. (C) Stage 2 MRONJ lesions are visible on both sides of the mandible and both sides of the maxilla. The patient experienced pain and had severe signs of infection, particularly bleeding, swelling and halitosis. The areas of MRONJ reflect the areas of pre-existing lesions from marginal periodontitis. (D) Panoramic radiograph of the patient with areas of horizontal and vertical bone loss in the molar and premolar regions of both sides of the mandible and maxilla, with only mild sclerotic changes. In addition, radio-opacities are visible in both maxillary sinuses and in the teeth-bearing areas at sites of restorative and prosthetic dentistry. (E) Signs of infection were reduced after 2 weeks of antibiotic treatment. Stage 3: woman aged 71 years with breast cancer and bone metastases who had received zoledronic acid 4 mg IV every 3–4 weeks for 4 years. (F) The patient developed stage 3 MRONJ with large areas of bone exposure and pus exudation on both sides of the maxilla, plus a chronic oroantral fistula formation with pus exudation from the maxillary sinus on the left-hand side. The patient had overt halitosis and 'spontaneous' tooth loss (most probably because of severe marginal periodontitis). The patient was receiving strong opioids and therefore did not experience oral pain until very late in the course of her disease; she reported difficulties drinking and had lost fluids through the nose (because of the oroantral communication on the left side). The oncologist referred the patient to the OMFS because of severe halitosis and pain. (G) Panoramic radiograph of the patient with structural bone loss on both sides of the maxilla and radio-opacities in both maxillary sinuses. Remnants of tooth alveoli with sharp bony edges can be detected despite loss of teeth many years before, indicating strong suppression of bone turnover. There are signs of severe marginal periodontitis and radiopaque calculus of the remaining teeth in the mandible, a root remnant in region 34 and a persisting alveolar socket in region 31. MRONJ, medication-related osteonecrosis of the jaw. IV: intravenous; MRONJ: medication-related osteonecrosis of the jaw; OMFS: oral and maxillofacial surgery.

outcomes for patients with MRONJ, a multidisciplinary approach is required involving dentists, nurses, primary care physicians, oncologists, oral and maxillofacial surgeons (OMFSs), and the patient. In addition, educational programs need to be adapted/implemented to improve interdisciplinary collaboration and understanding of the benefits and side effects of bone-modifying agents across dental and medical specialties. These initiatives should be tailored specifically to the role of each HCP in the prevention and management of ONJ.

The AAOMS stresses that priority should be given to the oncological treatment for patients with cancer and bone metastases at risk of developing MRONJ [14]. Physicians need to balance the risk of MRONJ with the benefit of bisphosphonates or denosumab in reducing the substantial risk of SREs [63]. A case-based review and application of recommendations from the 2015 guidelines of the International Task Force on ONJ [27,63] have advocated preventive measures to minimize the risk of MRONJ. A combination of preventive measures taken both before and during treatment with denosumab or bisphosphonates, as described below, can significantly reduce the risk of MRONJ [43,64,65]. For example, in a case series of 1243 patients receiving pamidronate, zoledronic acid or denosumab in a malignant setting, the incidence of MRONJ was reduced from 4.6% to 0.8% by the implementation of regular dental check-ups and improved oral hygiene [66].

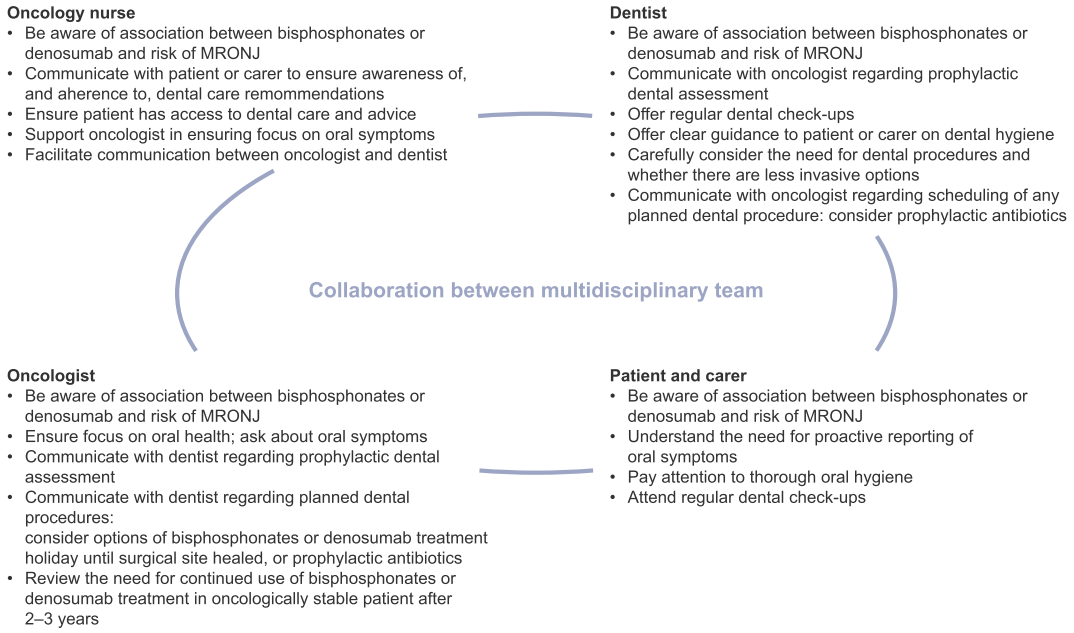

Fig. 4. Multidisciplinary approach to managing the risk of MRONJ.

Preventive measures taken before treatment with denosumab or bisphosphonates

It is important that physicians, dentists and patients consider preventive measures to reduce the risk of MRONJ (Fig. 4).

Discussing medication-related osteonecrosis of the jaw with patients

When patients with bone metastases are being considered for treatment with denosumab or bisphosphonates, it is important that the risk of developing MRONJ is clearly explained by HCPs in the context of maintaining skeletal health. SREs can cause considerable pain and reduce mobility and QoL [1–3,13], and the results of discrete-choice studies suggest that both patients and physicians consider that the benefits of the treatments outweigh the risk of developing MRONJ [67,68]. An analysis of the number of patients that would need to be treated with denosumab instead of zoledronic acid to prevent one additional SRE (7 patients), compared with the number that would need to be treated to induce one additional ONJ event (213) showed that the benefits of using denosumab substantially outweighed the risk of ONJ [19]. There are no data to suggest that prevention of ONJ should be different between similarly dosed bisphosphonates or denosumab, and the implementation of preventive strategies is identical with both types of therapy.

In addition to explaining the risk of MRONJ, preventive measures (Box 1) should be discussed with patients. The involvement of specialist nurses (e.g. oncology nurses or urology nurses for men with prostate cancer) should be considered when discussing MRONJ with patients to increase the opportunity to disseminate advice. If materials for patient education are available, these should be provided.

Oral assessments and other preventive measures

When in consultation with patients about the use of denosumab or bisphosphonates, it is essential that physicians carry out an oral examination, and take a brief dental history. In particular, it is important to identify local dental infections, especially those that involve the bone, such as marginal periodontitis and apical periodontitis. Other considerations might include the general status of a patient's dentition and, if there are dentures, whether these are ill-fitting and for how many years they have been worn. If a patient is undergoing chemotherapy, oncologists should briefly look for exposed bone when assessing for chemotherapy-induced oral mucositis.

Before initiation of denosumab or bisphosphonates, patients should also be assessed by their dentist, with a thorough examination of the oral cavity and radiographic assessment (e.g. panoramic radiographs; Box 1). While not currently indicated, a dental check at the time of diagnosis of a cancer that typically spreads to the bone may also be prudent in patients at high risk of developing bone metastases or likely to require chemotherapy early in their disease course [69] (i.e. advanced stage or clinically aggressive disease). In cases where antiresorptive therapy is likely to be needed at some time during the course of the patient's management, it would be helpful if they have already undergone any necessary dental treatment. This would result in less time pressure for dentists and OMFSs and less likelihood of a delay in antiresorptive therapy if/when urgently required at a later date. Nevertheless, formal cost-benefit assessments of such an intervention are currently lacking.

Preventive measures taken during treatment with denosumab or bisphosphonates

Several approaches can be taken during treatment with bisphosphonates or denosumab to prevent MRONJ (Box 2; Fig. 4). A key strategy is to encourage patients to maintain good levels of oral hygiene and to undergo 6-monthly dental check-ups. Both patients and HCPs need to remain vigilant for the signs and symptoms of MRONJ throughout treatment. All but the most minor dental procedures warrant the seeking of expert advice and the threshold for referral to an OMFS should be low in case of any uncertainty about the risk of MRONJ. In many cases, treatment will be suspended for major dental procedures (e.g. extraction and other procedures involving osseous injury) and restarted following soft-tissue closure. It should be noted, however, that evidence to support the practice of interrupting treatment in order to reduce the risk of ONJ development following dentoalveolar surgery is lacking. If considering treatment interruptions, it is relevant to note that denosumab does not become physically bound to the bone matrix and consequently is associated with low levels of accumulation [45,70]. Compared with bisphosphonates, which may remain covalently bound to the bone for many years [71], due to its mode of action, the effects of denosumab are reversed faster on suspension of treatment [72].

Box 1
Preventive advice and measures before starting treatment with denosumab or high bisphosphonates.

Preventive advice.

- The critical importance of maintaining good oral hygiene and avoidance of unnecessary dental surgery and dental infections should be explained to patients.
- Patients who do not have a dentist should be strongly encouraged to register with one or be referred to a hospital dentist or OMFS.
- Patients should be advised to inform their dentist that they are about to initiate denosumab or bisphosphonate treatment and to disclose the presence of any other MRONJ risk factors or comorbidities.
- Patients should be informed that they need to undergo a full dental assessment (including clinical and radiological assessment), as opposed to a standard check-up.
- Patients who have already commenced treatment with bisphosphonates or denosumab, but who have not yet received a full dental assessment or informed their dentist, should be encouraged to do so as soon as possible.
- Patients should be encouraged and feel comfortable to discuss any oral signs or symptoms with physicians or nurses.
- Patients should be educated on the signs and symptoms of MRONJ in order to facilitate early diagnosis.

Preventive measures.

- Dentists should carry out a full dental assessment (clinical and radiological).
- Any non-restorable teeth or teeth with a poor prognosis (e.g. with extensive periapical lesions or moderate-to-advanced periodontal disease [101]) should be removed and restorative procedures should be carried out on any teeth that are salvageable [14].*
- Any infections in the oral cavity should be treated appropriately (e.g. marginal periodontitis with systematic periodontal treatment, apical periodontitis with root canal treatment).*
- Patients who wear dentures are a risk of MRONJ as a consequence of local trauma caused by the dentures. Prostheses should be checked to ensure good positioning and any pressure points that have arisen should be treated.
- All dental surgery should be completed *before* antiresorptive therapy is initiated.
  - If an extraction is required, dentists should take good care of the wound or refer the patient to an OMFS. Achieving mucosal closure of an extraction site is sufficient in order to start antiresorptive therapy.
- If in doubt about the risk of MRONJ, dentists should refer patients to an OMFS for assessment [102].

*This measure is in line with routine dental procedure; avoidance of chronic infections is important regardless of whether a patient is receiving denosumab or bisphosphonates.
MRONJ, medication-related osteonecrosis of the jaw; OMFS, oral and maxillofacial surgeon.

Managing oral infections before and during treatment with denosumab or bisphosphonates

Dental infections are associated with MRONJ [73]; therefore, timely diagnosis and resolution of an underlying dental infection is a priority to prevent the condition. Furthermore, resolving infection may reduce the need for dental extraction, which is also associated with MRONJ. Dental extraction can be considered if the tooth is preventing resolution of the infection. Extractions should be carried out with the minimum level of trauma possible or be performed in a surgical setting according to published protocols to reduce the risk of subsequent MRONJ, which has a reported incidence of approximately 4% [26,74]. Tooth extractions in patients receiving denosumab or bisphosphonate treatment, especially in the oncological setting, should be performed under

Box 2
Preventive advice and measures during treatment with denosumab or bisphosphonates.

- Patients should be advised to maintain good levels of oral hygiene and to undergo regular dental check-ups (e.g. every 6 months) during treatment.
- Advice on the key signs and symptoms of MRONJ should be reiterated so that patients are vigilant for MRONJ signs and symptoms during therapy, and any available patient education materials should be provided, if this has not already been done.
- In line with the multidisciplinary approach, all HCPs involved in the treatment of patients with denosumab or bisphosphonates need to remain vigilant for the signs and symptoms of MRONJ during treatment.
- If patients experience dental problems while receiving treatment, they should be informed that they should contact their clinician and their dentist.
  - Minor dental procedures (fillings, inlays, crowns, scaling) can be carried out without interrupting treatment.
  - For other dental procedures, such as deep scaling or root canal (endodontic) treatment, expert advice needs to be obtained from an OMFS or experienced dentist, who may recommend the use of prophylactic antibiotics.
    - The timing of dental procedures should be determined with consideration of the pharmacokinetic profile of the treatment involved [14].
- If in doubt about the risk of MRONJ development, dentists should have a low threshold for referring patients to an OMFS for assessment and for any major dental procedures to be carried out.

HCP, healthcare professional; MRONJ, medication-related osteonecrosis of the jaw; OMFS, oral and maxillofacial surgeon.

antibiotic prophylaxis (e.g. amoxicillin/clavulanic acid) and accompanied by smoothening of sharp bony edges and closure of the wounds, and then monitored until complete mucosal healing is achieved [26].

Management of medication-related osteonecrosis of the jaw in patients with cancer and bone metastases

In general, there is a lack of well-designed prospective clinical trials – and indeed non-interventional studies – investigating MRONJ management approaches in patients with cancer and bone metastases. Furthermore, inconsistent outcome measures (e.g. patient QoL scales, mucosal healing and improvement of symptoms) are used across studies [75–78]. Overall, this means that it is challenging to reach a consensus on the most effective MRONJ management approaches available.

Patients who develop MRONJ should be referred to an OMFS or dental oncologist [79]. A pragmatic approach to the management of patients with MRONJ should be adopted (Fig. 1), with management of the malignant skeletal disease at the forefront of each patient's care. Conservative management is recommended for AAOMS stage I MRONJ, supplemented with surgical approaches as appropriate for more severe cases.

Conservative management of medication-related osteonecrosis of the jaw

The signs and symptoms of MRONJ, such as pain and those caused by underlying infection, can be effectively managed in the majority of patients using a conservative approach, particularly at stage 1 [14,27]. However, mucosal closure is rarely achieved without surgery and prolonged treatment is often required [75–78]. Some or all of the following management strategies can be used [14,27]: maintenance of optimal oral hygiene; elimination of active dental and periodontal disease using topical antibacterial mouth rinses (e.g. chlorhexidine); and systemic antibiotic therapy.

Surgical management of medication-related osteonecrosis of the jaw

Historically, MRONJ management guidelines discouraged surgical intervention based on a lack of consistent evidence of positive response [58,80]. For cases in which surgery was conducted, guidance encouraged superficial removal of damaged tissue to relieve irritation [58,81]; thus, the potential benefits of surgical intervention may have been limited by incomplete removal of necrotic bone and insufficient mucosal coverage. Recommendations were based on sparse data – not entirely specific to MRONJ – and a suspicion that the main cause of MRONJ could be surgical trauma rather than infection. However, with increasing experience over recent years, more evidence has emerged to support the use of surgery to treat MRONJ [75,82–84]. This management approach may be suitable for patients for whom conservative measures have not been, or are unlikely to be, successful or appropriate. Current AAOMS guidance recommends debridement to relieve soft tissue irritation and infection control at stage 2, with resection considered at stage 3 (Fig. 1) [14]. Overall consideration should be given to the goals of therapy, a patient's cancer prognosis and any barriers to surgery in order to avoid over- or under-treatment. Barriers to surgery include the temporary decrease in QoL during convalescence, the risk of treatment failure, the possibility of complications (e.g. risk of infection), the need for (extended) hospitalization, uncertain implications of necessary interruptions to chemotherapy, and any costs for the patient.

Evidence from well-designed, prospective, randomized clinical trials is lacking and it remains unclear which subset(s) of patients will derive most benefit from surgical intervention. However, indirect comparison of empirical data and clinical series in both low- and high-risk patients suggests that surgery may be superior to conservative treatment of MRONJ in achieving mucosal healing [75,82–86]. A recent report based on findings from 141 patients who underwent surgical management of ONJ and were being treated with denosumab or bisphosphonates for cancer (n = 83) or osteoporosis (n = 58) has shown that surgery (using primary closure) has a high cure rate: 93% of 141 patients who underwent surgery were cured, whereas in 63 patients who received conservative treatment, the cure rate was 17% [82]. In these patients, 'cure' was defined as the absence of symptoms, with no clinical examination evidence or radiographical evidence of MRONJ. It is also important to note that treatment allocation was not randomized.

The complete removal of necrotic bone, smoothing of sharp bony edges and meticulous wound closure, accompanied by perioperative antibiotic treatment, is generally considered to be the most suitable approach to achieve MRONJ healing [23,76,77,87]. A major challenge of surgical treatment is to distinguish between viable and necrotic bone [77,88] so that the minimum amount of bone possible is removed. This is important to facilitate healing, to limit any weakening of the jawbone and to maximize the chances of dental or prosthetic rehabilitation [77]. The demarcation between necrotic and viable bone is often unclear and it is not possible to standardize surgical techniques; therefore, much is dependent on the surgeon's skill and expertise [77]. However, recent innovative approaches have combined surgical treatment with intraoperative visualization of fluorescent patterns of viable and non-viable bone (fluorescence-guided surgery) to improve surgical outcomes [76,77,87,89].

Traditionally, surgery was primarily indicated after the formation of a bony sequestrum. However, surgery may be effective for the treatment of MRONJ at any disease stage [14,27,75,77,90]. Recent study findings suggest that surgery to remove necrotic bone, smoothing of sharp bony edges and wound closure may be the treatment of choice at early stages of MRONJ (e.g. stages 1 and 2). At later stages, when there is extensive necrosis (e.g. stage 3), patients may also be treated by the removal of necrotic bone, smoothing of sharp bony edges and wound closure; some cases may require segmental/continuity resections. Other cases may be best treated by clinical monitoring. The choice of approach adopted primarily depends on the underlying condition and the status of the patient [91].

The AAOMS 2014 guidelines advise that, if they are a persistent source of soft-tissue irritation, loose teeth should be extracted and areas of necrotic bone should be removed or recontoured [14]; however, while superficial bone debridement may relieve symptoms, it rarely leads to mucosal healing and is likely to result in poor surgical outcomes. Some evidence suggests that better outcomes are achieved following larger amounts of bone removal than after limited debridement [92].

While some physicians recommend interrupting treatment with bisphosphonates or denosumab for 2–3 months (i.e. a drug holiday) to allow local treatment and healing following surgery, there is no evidence to support the optimal timing or the effectiveness and safety of this approach. Hypothetically, patients with MRONJ who have been treated with denosumab may respond better to a treatment holiday than those who have received zoledronic acid owing to the different pharmacokinetic properties of the drugs. Zoledronic acid and other potent bisphosphonates have a strong affinity for bone and are slowly released from skeletal tissue (bisphosphonates have a terminal half-life of approximately 11 years) [93]. Denosumab has a half-life of 28 days and does not bind to bone [7]. However, to date, no randomized study data have been published to support the practice of treatment holidays and they are not recommended by the AAOMS [14,27]. There seems to be a general agreement among OMFSs and oncologists that treatment can be continued after mucosal healing. In the integrated analysis of three phase 3 studies of denosumab and zoledronic acid for patients with bone metastases associated with solid tumors or multiple myeloma, healing of confirmed cases of MRONJ (defined as healed mucosa in the absence of symptoms) following cessation of treatment was reported in about 40% of patients receiving denosumab and about 30% of those receiving zoledronic acid [19]; the median time to resolution was 8.0 months for denosumab and 8.7 months for zoledronic acid). As yet,

however, data remain limited on this topic. Overall, there is an unmet need for data from prospective, controlled studies to inform our understanding of the best approaches to the management of MRONJ.

Depending on the choice of treatment and clinical evolution of the ONJ lesion, careful follow-up is recommended. In general, patients should be seen every 3 months, but more frequent office visits may be required after surgical intervention or initiation of antibiotics (every 2–3 weeks) [94].

Current controversies and uncertainties

The elusive nature of the pathogenesis of MRONJ hampers the development of improved therapeutic approaches. Although it is universally accepted that bone trauma has a pivotal role in the process leading to MRONJ, evidence is growing that infection also plays a prominent role [26,49,73,85,95,96]. The multitude of local inflammatory mediators released during infection, the resulting local acidic milieu, and the impact of medication on the bone microenvironment may all be important in the pathogenesis of MRONJ [95,96]. In the absence of treatment with bisphosphonates or denosumab, it is rare for patients with dental infection to develop ONJ [23,97]. Previous observations have described over-suppression of jawbone turnover, a higher re-modeling rate in the jawbone than in the axial or appendicular skeleton [14,49,50], and the paradoxical finding that bone turnover is greater in the maxilla than the mandible, despite most cases of MRONJ occur in the latter [23,46,98]. These findings may need reconsideration from the perspective of the changing demands on the jaw bone microenvironment in response to local stresses. For example, neither denosumab nor bisphosphonates should suppress jawbone turnover sufficiently to induce MRONJ in the absence of other triggers, such as infection or micro-fractures [46–48,98]. However, the bone turnover mechanism may become stretched beyond its capabilities when latent infection is present, and may fail altogether after direct bone trauma, leading to clinically overt MRONJ. Parallels can be drawn with the occasional occurrence of osteonecrosis of the external auditory canal in patients receiving bone-modifying agents [6,99]. Like the oral cavity, the external auditory canal has only a very thin integument layer separating bone from a heavily bacterially colonized environment; thus a similar pathophysiological mechanism may be hypothesized [100].

Conclusions

There has been increasing recognition of MRONJ as an adverse side effect of treatment with denosumab or bisphosphonates, particularly in the oncological context. Dento-alveolar infections and trauma of the jawbone appear to play a key role in MRONJ pathogenesis. The overall benefit–risk balance for denosumab and bisphosphonates is positive; therefore, the prevention and treatment of dental infections before and during treatment with these agents is crucial in order to avoid the development of MRONJ while facilitating their use.

Optimizing the management of MRONJ can be challenging. Treatment protocols are complex and need to be adapted to the individual patient. Preventive measures are effective and should be discussed among the multidisciplinary team (HCPs, including dentists, and their patients) before and during treatment with denosumab or bisphosphonates. Early data on MRONJ management showed that conservative/non-surgical treatment improves symptoms but results in variable and suboptimal rates of mucosal closure. Increasing experience with surgical approaches suggests that surgery may be beneficial when symptom management and mucosal healing are the ultimate goals, based on indirect data comparisons. Further evidence from well-designed, prospective, randomized clinical trials is awaited, and it remains unclear which subset(s) of patients will derive most benefit from surgical intervention or what the optimal treatment sequence would be. There remains a need for robust data to guide HCPs in improving MRONJ treatment decisions and outcomes for patients.

Improvements in communication between HCPs – and indeed between HCPs and their patients – are needed to identify barriers to prevention and optimal management of MRONJ. Further research is required to provide clarity regarding MRONJ pathophysiology, risk factors, treatment and other management strategies. Overall, a multidisciplinary, pragmatic approach to the prevention and management MRONJ should be adopted, giving priority to patients' QoL and management of their skeletal malignant disease.

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