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# Medication – related osteonecrosis of the jaws. The first reported cases in the Baltic States and a literature review

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## SUMMARY

*Introduction.* Medication–related osteonecrosis of the jaws (MRONJ) is a severe side effect of antiresorptive or antiangiogenic therapy that manifests as an exposed bone, accompanied by clinical signs of infection, persisting for more than 8 weeks, without history of radiation therapy or metastases to the jaws. The aim of the study was to present first MRONJ cases in Lithuania and review trends in the modern research literature on the subject.

*Materials and methods.* We retrospectively reviewed patient charts with a diagnosis of "Inflammatory conditions of the jaws" treated in Vilnius University Hospital Žalgiris Clinic, Department of maxillofacial surgery in 2007-2014. Patients diagnosed with MRONJ were selected for the study. Demographic data, characteristics of the disease and treatment modalities were analysed.

*Results.* Nine cases (five male and four female) of MRONJ were analysed. The mean patient age was 69±7,9 years. Predominant primary malignancy was prostate cancer. Osteonecrotic lesions were located both in maxilla and mandible. In all cases we started with a conservative treatment first. After the antibiotic therapy with or without sequestrectomy, the condition of all patients stabilized and improved to stage I MRONJ.

*Conclusion.* MRONJ is a disturbing condition resulting in a severely worsened quality of life in the affected patients. This is the first case series of successfully treated patients suffering from stage II or III MRONJ in the Baltic States. A more comprehensive understanding of MRONJ will hopefully allow clinicians to enhance accuracy in risk assessment and forecast positive and negative outcomes of antiresorptive or antiangiogenic therapy.


**Keywords:** bisphosphonate-associated osteonecrosis of the jaw, medication-associated, medication-induced, bisphosphonates, medication-related.

## INTRODUCTION

Osteonecrosis of the jaws is a severe side effect of antiresorptive or antiangiogenic therapy that manifests itself as an exposed bone accompanied by pain, swelling, and purulent secretions. In the newest position paper published in 2014, The American Association of Oral and Maxillofacial Surgeons (AAOMS) suggested to change the previous term Bisphosphonate-Related Osteonecrosis of the Jaw (BRONJ) to Medication-related osteonecrosis of the jaw, as not only bisphosphonates but also denosumab or antiangiogenic agents (sunitinib, sorafenib, bevacizumab, sirolimus) may cause the same condition. According to the AAOMS, medication-related osteonecrosis of the jaw (MRONJ) is confirmed when all of the following characteristics are present: 1. Current or previous treatment with bisphosphonate, denosumab or antiangiogenic agent; 2. Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for more than 8 weeks; 3. No history of radiation therapy to the jaws or obvious metastatic disease to the jaws (1).

Until the year 2001 there were only isolated BRONJ case reports. In 2003 there were 3 publications concerning BRONJ, among those by Marx RE

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who reported 36 BRONJ cases and called it a growing epidemic (2). A leaping numbers of publications on the subject proved the term to actually be true. A search on PubMed database by the keywords: "bisphosphonate", "medication", "osteonecrosis", "jaws" at the time of editing this article resulted in total of 1390 articles (of them 308 reviews, 252 free full text).

To the best of our knowledge there are neither BRONJ or MRONJ prevalence data nor any reported relevant cases yet available in the Baltic States.

Bisphosphonates have been authorized for use in Lithuania since 2001 and denosumab was introduced in 2011. Antiangiogenic medications have been used since 2005. Regretfully, patients receiving antiresorptive and antiangiogenic agents are not ordinarily monitored for MRONJ. Patients may be even not aware whether or not they are taking these agents being involved in some blind or double-blind clinical trials. MRONJ clinical presentation is not immediate; at least one year of intravenous and three years of peroral continuous antiresorptive drug use is needed for MRONJ development.

The aim of the study was to present first MRONJ cases in Lithuania and to review the trends in the modern research literature on the subject.

## MATERIALS AND METHODS

We retrospectively reviewed all patient files with an ICD-10 (10th Edition of International Classification of diseases) code K10.2 (Inflammatory Conditions of the Jaws) treated in the Department of Maxillofacial Surgery at Vilnius University Hospital Žalgiris Clinic from 2007 till 2014. Patients that fulfilled the AAOMS diagnostic criteria of MRONJ were selected for the study. The first patient who came to our department with BRONJ in 2007 was excluded from the study, as she refused any medical treatment. The data of all the other patients diagnosed with MRONJ were analysed and included into the study. We collected the demographic data (age at the time of admission, sex, concomitant diseases), analysed characteristics of the MRONJ (the type of therapeutic agent which induced the disease, the localization, extent and stage of MRONJ) and treatment modalities applied in our clinic.

The stage of the disease was set according to the staging system proposed by AAOMS:

*Patients at risk:* no apparent necrotic bone in asymptomatic patients who have been treated with antiresorptive or antiangiogenic agents.

*Stage 0:* patients with no clinical evidence of necrotic bone, but who present with nonspecific symptoms or clinical and radiographic findings.

*Stage 1:* exposed and necrotic bone or fistulas that probe to bone in patients who are asymptomatic and have no evidence of infection.

*Stage 2:* exposed and necrotic bone or fistulas that probe to bone in patients with pain and clinical evidence of infection.

*Stage 3:* exposed and necrotic bone or fistulas that probe to bone in patients with pain, infection, and one or more of the following: exposed necrotic bone extending beyond the region of alveolar bone (i.e., inferior border and ramus in the mandible, maxillary sinus and zygoma in the maxilla); pathologic fracture; extraoral fistula; oral antral/oral nasal communication; osteolysis extending to the inferior border of the mandible or sinus floor (1).

## RESULTS

Up till now there were 9 cases of MRONJ treated at Vilnius University Hospital Žalgiris Clinic. In March 2007 we encountered this condition for the first time. The patient was a 54-year-old female treated with BPs (Pamidronic acid) in Germany for metastatic breast cancer of the spinal column. She came to our clinic complaining of exposed mandibular bone in the region of teeth #42 – #45 (acc. FDA). Teeth were still present. At this time BRONJ stage 1 was diagnosed, but the patient was excluded from our study as she refused any medical treatment, was not admitted to our department and was also lost to follow up.

All other MRONJ patients were included in the study. The patient information is presented in Table 1. The mean patient age was 69±7.9 years. Five of our patients were male and four of the patients were female. 6 patients treated in our clinic because of MRONJ received intravenous bisphosphonates and 2 were treated with denosumab due to metastatic disease of the skeleton. Two patients received a combination of zolendronate and pamidronate, one patient was treated with zolendronate only. In three cases, the name of bisphosphonate could not be specified as these patients participated in clinical trials on testing the efficacy of bisphosphonates in other clinics and did not know the name of the drug they were taking. The leading malignancy causing bony metastases in our group was prostate cancer (5 cases), followed by breast cancer (2 patients) and uterine cancer (1 patient). One patient had an 8-year-long therapy with peroral ibandronic acid because of osteoporosis. There were no cases of MRONJ induced by antiangiogenic agents.

5 patients had MRONJ of maxilla, 3 – of the mandible, and in 1 patient both jaws were affected.

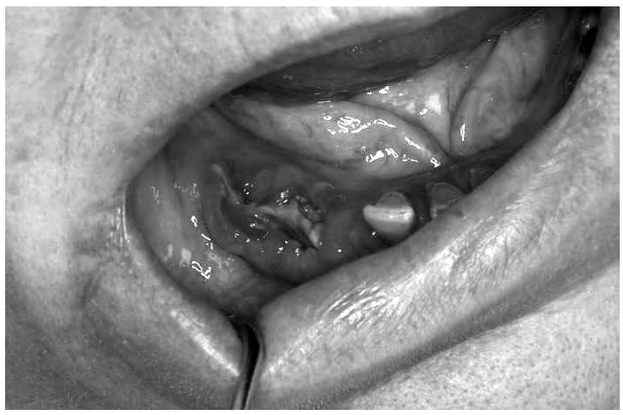

**Fig. 1.** Stage II MRONJ - exposed necrotic bone in the right mandible at presentation

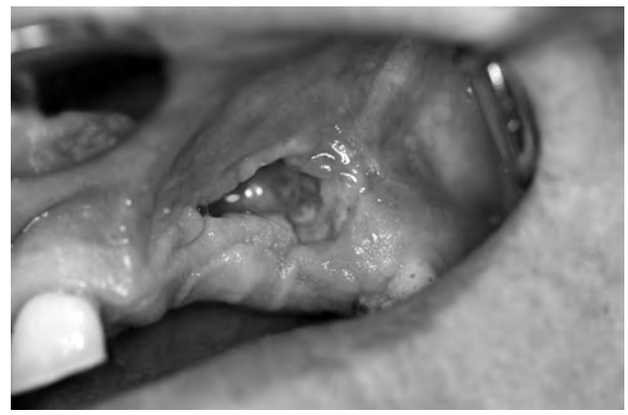

**Fig. 2.** Stage II MRONJ. Purulent discharge and bony defect in the left maxilla.

In all cases the orthopantomogram (OPT) or/and a cone-beam computed tomography (CBCT) were performed to define the extent of MRONJ more precisely. The extent of the necrosis was ranging from 1×0,5 cm (patient number 7) to the area involving mandibular body from the tooth #45, angle and ramus (patient number 6). All patients except two were diagnosed with MRONJ stage II, i.e. they had developed an exposed, necrotic bone, were suffering from pain and had clinical signs of infection (Figures 1, 2). Patients 6 and 9 presented with the most severe case of MRONJ stage III. Patient number 6 had an exposed maxillary and mandibular bone in the posterior region on the right side, osteolysis extending to the inferior border of the mandible and infection spread to the submandibular space (Figure 3). In patient number 9, there was necrosis of the left maxilla (area of tooth 26) with destruction of the left maxillary sinus floor and infection spread to the left maxillary sinus. The changes are clearly seen in a CBCT scan (Figure 4)**.**

In all cases treatment was started in a conservative mode. Patients were prescribed oral antimicrobial rinses (*chlorhexidine 0,12% qds*) combined with antibiotic therapy. According to culture and sensitivity test results patients were also prescribed *benzylpeni-*

**Table 1.** Patient summary

| Pat. No. | Age | Sex | Initial Disease | Location | Medication prescribed | Length of antiresorptive therapy | MRONJ stage | Size of lesion | Surgical treatment | | Antibiotics |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | Bone removed | Flap | |
| 1. | 63 | M | Prostate Ca | L Mx | D | 2 years | II | Teeth #21 – #23 | Yes | Yes | L, Cd, M |
| 2. | 70 | M | Prostate Ca | L, R Mx | NS | 5 years | II | Teeth #15 – #24 | No | No | P, Cd, M |
| 3. | 62 | F | Uterine Ca | R Md | NS | 3 years | II | 1.5 cm (edentulous Md) | Yes, ~3 cm | No | P |
| 4. | 73 | M | Prostate Ca | R Mx | NS | 2,5 years | II | R Mx sinus | No | No | P |
| 5. | 69 | M | Prostate Ca | L Mx | D | 2 years | II | Tooth #22 | Yes | Yes | P, L |
| 6. | 57 | F | Breast Ca | R Mx, R Md | Z, Pam | 1,5 years | III | Teeth #18-17, #47-45, R Md ramus | No | No | P,M |
| 7. | 84 | F | Osteo-porosis | L Md | I | 8 years | II | Tooth #36 (1×0.5 cm) | Yes | No | P |
| 8. | 69 | F | Breast Ca | L Md | Z, Pam | 2 years | II | Tooth #38 | Yes | No | L |
| 9. | 74 | M | Prostate Ca | L Mx | Z | 8 years | III | Tooth #26, maxillary sinus | Yes | Yes | Cf |

Sex: M – male, F – female. Localization: L – left, R – right, Mx – maxilla, Md – mandible. BP prescribed: D – denosumab, NS – not specified. Pam – pamidronate, I - ibandronate, Z - zolendronate Antibiotics: P – penicillin; L – lincomycin; Cd – clindamycin; M – metronidazole, Cf – cefuroxime

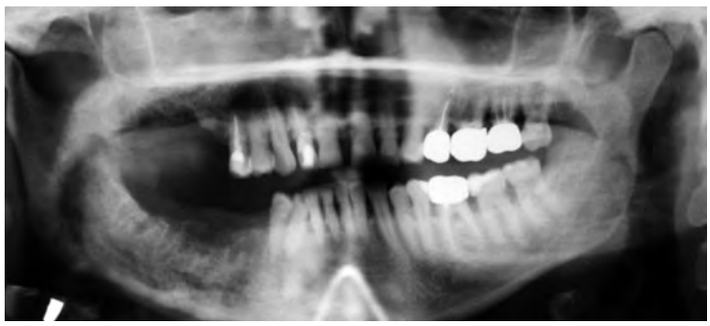

**Fig. 3.** The OPT of patient number 6. The osteolysis of the mandibular body from the tooth #45, angle and ramus, spreading to the inferior border of the mandible, is clearly seen. There are also radiologic signs of osteonecrosis in the right maxilla, area of teeth #17-#18.

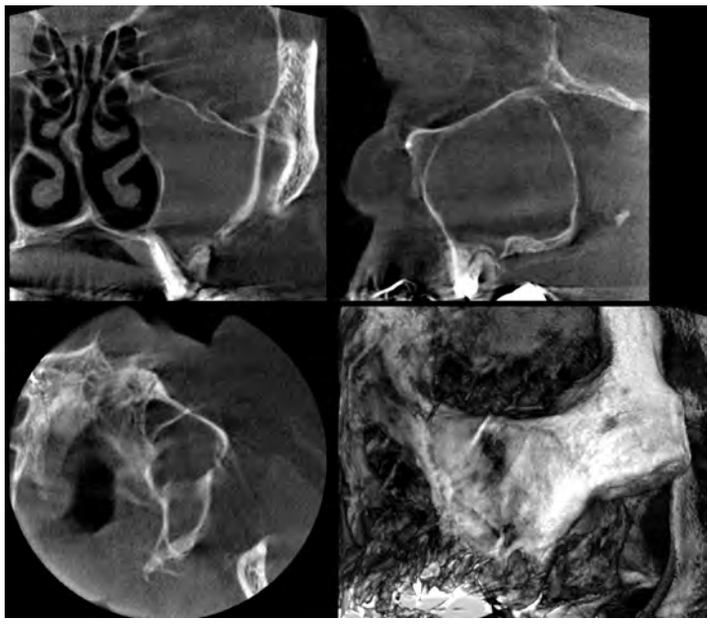

**Fig. 4.** A CBCT scan of patient number 9. Signs of osteonecrosis in the left maxilla (area of tooth #26), destruction of left maxillary sinus floor, lateral wall and infection spread into the left maxillary sinus.

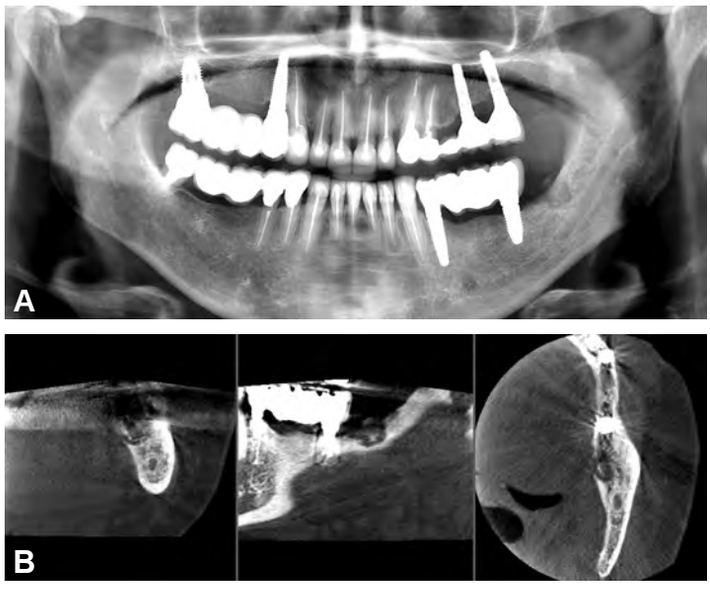


**Fig. 5.** A – an OPT of patient number 8. There are signs of osteonecrosis in the area of tooth #38 which was extracted 2 months after the patient started BP therapy. The area of dental implants in the region of teeth #37-#34 is intact; B – the same is confirmed with a CBCT scan.

*cillin 1.000.000 IU qds iv, lincomycin 0,6 tid iv, clindamycin 0,3 tid po, metronidazole 0,5 tid iv* or *po* or *cefuroxime 0,75 tid iv*. In five cases debridement of necrotic bone was performed under local anesthesia. All efforts were taken to ensure that the procedures are as non-invasive as possible. Mucoperiosteal flap was raised in two cases. For patient number 6 surgery was not an option because of poor general medical condition. Patient number 9 had a sequestrectomy and debridement in a combination with functional endoscopic sinus surgery under general anesthesia.

On discharge from hospital the condition of all patients was stabilized and improved to MRONJ stage I.

## DISCUSSION

Oral bisphosphonate preparations are most commonly utilized in treating osteoporosis, especially in postmenopausal females (3). Injectable BPs, as well as Receptor Activator of Nuclear factor Kappa-B Ligand (RANKL) inhibitor denosumab, are used primarily in the treatment of metastatic bone disease (first publications since 1980 (4)), although protocols for osteoporosis and Paget's disease were already approved by the FDA (Food & Drug Administration (US)). (5) Use of the intravenous bisphosphonates is considered the standard of care in the treatment of hypercalcemia and osteopenia associated with metastatic malignancies (6, 7).

BP's and other antiresorptive drugs, such as denosumab, inhibit osteoclast differentiation and function and increase apoptosis, all leading to decreased bone resorption and remodelling (1). The overall effect is a decrease in bone turnover and inhibition of the bone's reparative ability (8-10). It is known that alveolar bone of the jaws has very high turnover rates. Dixon et al. (11) stated that alveolar crest has a remodelling rate 10x of tibia, 5x of mandible at level of inferior alveolar canal and 3.5x of mandible at inferior border (11). These high turnover rates might be causing high bisphosphonate accumulation in alveolar bone. Besides, the jaw bones are separated from a trauma-intense and microbiologically diverse oral environment by thin mucosa and periosteum (12). Injury to the bone in patients receiving BP's or denosumab via tooth extraction, dental surgery, or mechanical trauma is thought to initiate medication-related osteonecrosis of the jaw (MRONJ) by surpassing the repair capability of the hypodynamic

bone, resulting in localized bone necrosis (13). The antiangiogenic property of bisphosphonates and other medications and the presence of other comorbid factors may promote the risk for or persistence and progression of this condition (14).

Intravenous (IV) bisphosphonate exposure in the setting of managing malignancy remains the major risk factor for MRONJ. According to case series, case-controlled studies, and cohort studies, estimates of the cumulative incidence of MRONJ have ranged from 0,8% to 12% (15-23). Patients receiving oral bisphosphonate therapy are at a considerably lower risk of MRONJ than cancer patients treated with monthly IV bisphosphonates. According to the data from the manufacturer of alendronate (Merck, Whitehouse Station, NJ), the incidence of MRONJ was calculated to be 0.7/100000 person-years of exposure (24). Surveillance data from Australia estimated the incidence of MRONJ for patients treated weekly with alendronate as 0,01% to 0,04% (25). In a survey study of more than 13.000 Kaiser-Permanente members, the prevalence of MRONJ in patients receiving long-term oral bisphosphonate therapy was reported at 0.06% (1:1700) (26). The available data suggests that the risk of MRONJ for patients receiving IV bisphosphonates is significantly greater than the risk of MRONJ for patients receiving oral bisphosphonates. We can support these statements with our case series, because all but one MRONJ patients treated in our department also received intravenous antiresorptive medications (BP's or denosumab).

Other risk factors for MRONJ development are categorized as drug-related, local, demographic or systemic, genetic and preventative factors (1, 27).

**Drug-related risk factors**

It is known that the potency of BP's differs (e.g. zolendronate (Zometa®) is more potent than pamidronate (Aredia®), and pamidronate (Aredia®) is more potent than the oral bisphosphonates) and the longer the duration of using antiresorptive agents, the higher the risk of developing MRONJ (16, 23, 28-30). In our patient group, patients received one or combination of different intravenous BP's or denosumab for at least 2 years. Patient 7 who was prescribed with an oral BP was taking the medication monthly for 8 years.

**Local risk factors**

*Dentoalveolar surgery*, including, but not limited to extractions, dental implant placement, periapical surgery, periodontal surgery (involving osseous injury) (15, 23, 30). Patients receiving intravenous bisphosphonates and undergoing dentoalveolar surgery are at least 7 times more likely to develop MRONJ than patients who are not undergoing dentoalveolar surgery (23, 30). The majority of our patients developed symptoms of MRONJ after teeth extractions. There was one interesting case (patient number 8) in which osteonecrosis involved the area of tooth #38 that was extracted two years ago, two months after the first injection of zolendronate. The patient also had dental implants placed in the area of teeth #34 - #37 at the same time. However, there were no radiologic signs of osteonecrosis in the implant area (Figure 5).

*Local anatomy:* lingual tori and mylohyoid ridge in the mandible, palatal tori in the maxilla (1). It has been observed that lesions are found more commonly in the mandible than the maxilla (2:1 ratio) and more commonly in areas with thin mucosa overlying bony prominences such as tori, bony exostoses, and the mylohyoid ridge (31-33). Our study is not that consistent with the data from the literature, as there were 5 case of MRONJ in maxilla, 3 cases – of the mandible and in one case both jaws were affected. Interestingly, all our male patients had lesions in maxilla and 3 female patients presented with osteonecrosis of the

**Table 2.** Treatment strategies according to the MRONJ stage (proposed by AAOMS)

| Stage of MRONJ | Treatment strategies* |
|---|---|
| At risk | No treatment indicated<br>Patient education |
| Stage 0 | Systemic management, including use of pain medication and antibiotics |
| Stage I | Antibacterial mouth rinse<br>Clinical follow-up on a quarterly basis<br>Patient education and review of indications for continued bisphosphonate therapy |
| Stage II | Symptomatic treatment with oral antibiotics<br>Oral antibacterial mouth rinse<br>Pain control<br>Debridement to relieve soft tissue irritation and infection control |
| Stage III | Antibacterial mouth rinse<br>Antibiotic therapy and pain control<br>Surgical debridement or resection for longer-term palliation of infection and pain |

*Regardless of disease stage, mobile segments of bony sequestrum should be removed without exposing uninvolved bone. Extraction of symptomatic teeth within exposed necrotic bone should be considered because it is unlikely that extraction will exacerbate the established necrotic process.

mandible. One female patient had both maxillary and mandibular lesions. We did not find any connection between the gender and the affected jaw in any literature source.

*Concomitant oral disease:* cancer patients exposed to intravenous bisphosphonates with a history of inflammatory dental disease (e.g., periodontal and dental abscesses) are at a 7-fold increased risk of developing MRONJ (23).

**Demographic and systemic factors**

Increasing age is consistently associated with MRONJ, giving a 9% increased risk for every passing decade (17, 29, 30, 34-37). Race was reported in 1 study to be a risk factor, with whites having an increased risk of MRONJ compared with blacks (30). Though found in both sexes, in research references MRONJ in females has been found more frequently than in males which is likely a reflection of the large number of cases reported in breast cancer patients. With postmenopausal osteoporosis as an indication for bisphosphonate use, a large percentage of the female population may also be at risk for developing MRONJ (39). In our case series, the mean patient age was 69±7,9 years. This is consistent with the data produced by other researchers that MRONJ is strongly correlated with the age factor (17, 29, 30, 34-37). In contrast with the literature, 5 out of 9 our patients were male. Therefore predominant malignancy in our patient group was prostate cancer, the most common cancer in men (39).

Other systemic factors or conditions (i.e., renal dialysis, low hemoglobin, obesity, and diabetes) were variably reported to increase the risk of MRONJ (34, 40, 41). Malignancy type was not significantly associated with an increased risk of MRONJ (24), although the presence of metastatic disease reached near statistical significance (P=0.051) in the report by Wessel et al. (40). A few current studies have noted an increased risk of MRONJ among patients exposed to chemotherapeutic agents (i.e., cyclophosphamide, erythropoietin, and steroids) (34, 36). Others, however, have failed to confirm the association between chemotherapeutic agents and MRONJ risk (15, 17, 37, 40). Wessel et al (40) reported an increased risk of MRONJ among tobacco users, but no increased risk was associated with alcohol exposure.

**Genetic factors**

Sarasquete et al (42) demonstrated that genetic perturbations (i.e., single nucleotide polymorphisms, in the cytochrome P450-2C gene [CYP2C8]) were associated with an increased risk of MRONJ among multiple myeloma patients treated with IV bisphosphonates.

**Preventive factors**

Studies have suggested that manipulation of IV bisphosphonate dosing might be effective in reducing skeletal-related events and minimizing MRONJ risk (37). In addition, preventive dental interventions before initiating IV bisphosphonate treatment can also effectively reduce, but not eliminate, the risk of MRONJ.

Treatment of MRONJ is stage-dependent (27). The treatment modalities range from observation, symptomatic treatment and antimicrobial rinsing for stage 0 or I patients to antibiotics and surgical treatment (debridement of the necrotic bone or even resection of the jaw) for stage II or III cases (Table 2). Irrespective of the stage of disease, mobile segments of bony sequestrum should be removed without exposing uninvolved bone (1). The extraction of symptomatic teeth within exposed, necrotic bone should be considered as it is unlikely that the extraction will exacerbate the established necrotic process. Patients at risk of, or with established MRONJ can also present with other common clinical conditions not to be confused with MRONJ. Commonly misdiagnosed conditions can include alveolar osteitis, sinusitis, gingivitis/periodontitis, caries, periapical pathologic findings, and temporomandibular joint disorders (27). Appropriate treatment should be started as soon as diagnosis is established.

In our case series, all patients except two were diagnosed with MRONJ stage II, i.e. they had developed an exposed, necrotic bone with clinical evidence of the infection. Two patients were diagnosed with the stage III MRONJ. Patient number 6 had osteolysis extending to the inferior border of the mandible and infection spread in the submandibular space and patient number 9 presented with the osteonecrosis of the left maxilla, destruction of the maxillary sinus floor and infection spread into the maxillary sinus. Despite the stage of MRONJ, we started the treatment in a conservative mode in all our cases. Patients were prescribed with oral antimicrobial rinses combined with antibiotic therapy which was selected according to culture and sensitivity test results. We performed bone debridement only in cases when a clear bony sequestrum could be observed in OPT or CBCT scans. In case number 9, the functional endoscopic sinus surgery was performed additionally because of infection spread to the maxillary sinus. All these treatment modalities were selected according to international MRONJ treatment standards and they proved to be successful, as the condition of all patients was stabi-

lized and improved to MRONJ stage I on discharge from the hospital.

Oncology patients benefit greatly from the therapeutic effects of IV bisphosphonates due to their ability to control bone pain and the incidence of pathologic fractures. Discontinuation of IV bisphosphonates does not ensure any short-term benefit. However, if systemic conditions permit, long-term discontinuation might be beneficial in stabilizing established sites of MRONJ, reducing the risk of new site development, and reducing clinical symptoms (43-45). The risks and benefits of continuing antiresorptive therapy should be determined only by the treating oncologist in consultation with the oral and maxillofacial surgeon and the patient. Discontinuation of oral bisphosphonate therapy in patients with MRONJ has been associated with gradual improvement in clinical disease (46). Discontinuation of oral bisphosphonates for 6 to 12 months can result in either spontaneous sequestration or resolution after debridement surgery. If systemic conditions permit, modification or cessation of oral bisphosphonate therapy should be done in consultation with the treating physician and the patient.

## CONCLUSION

MRONJ is a disturbing condition resulting in a severely worsened quality of life in the affected patients. This is the first case series of successfully treated patients suffering from stage II or III MRONJ in the Baltic States. A more comprehensive understanding of MRONJ will hopefully allow clinicians to enhance accuracy in risk assessment and forecast positive and negative outcomes of antiresorptive or antiangiogenic therapy.

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