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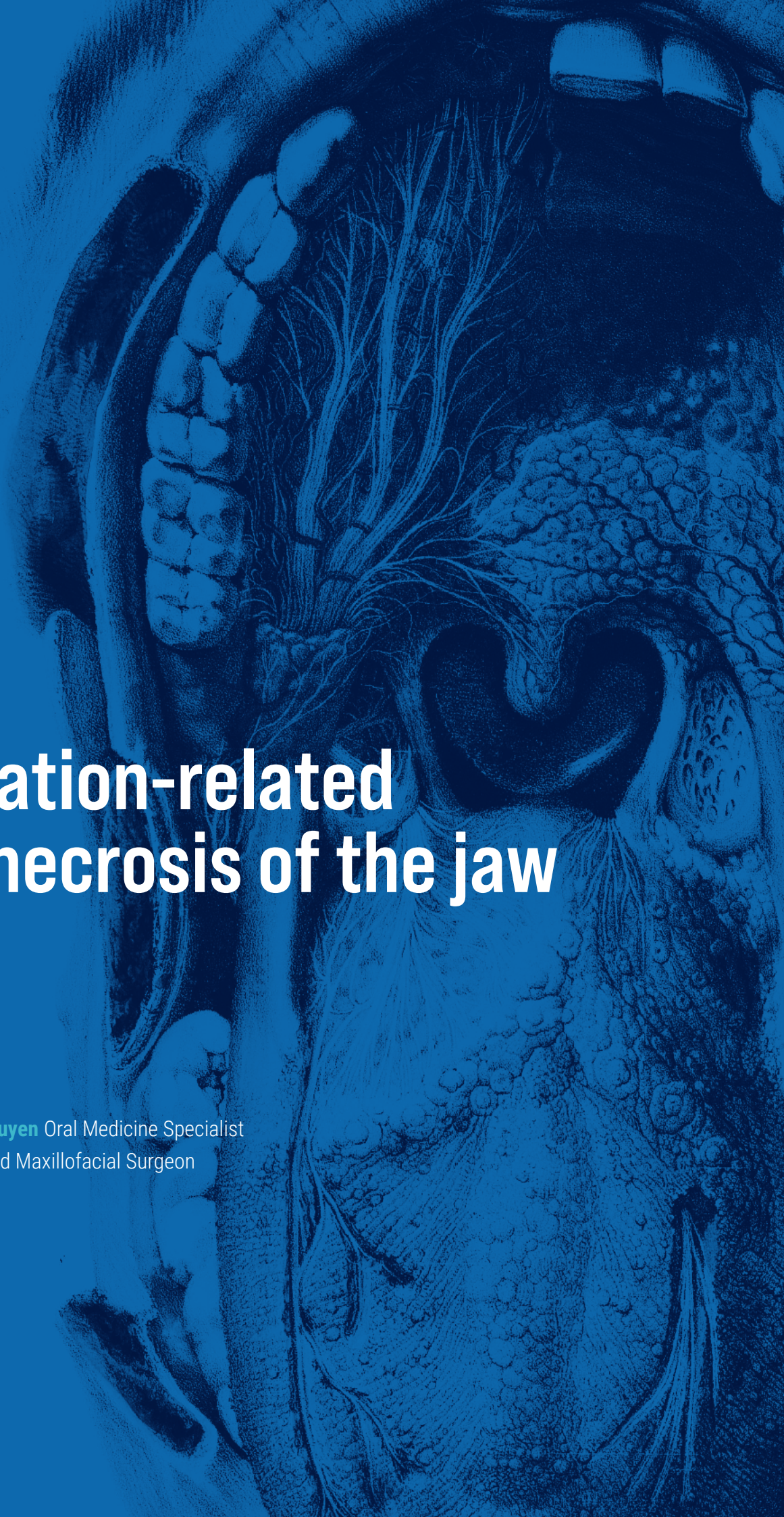

Medication-related osteonecrosis of the jaw

(MRONJ)

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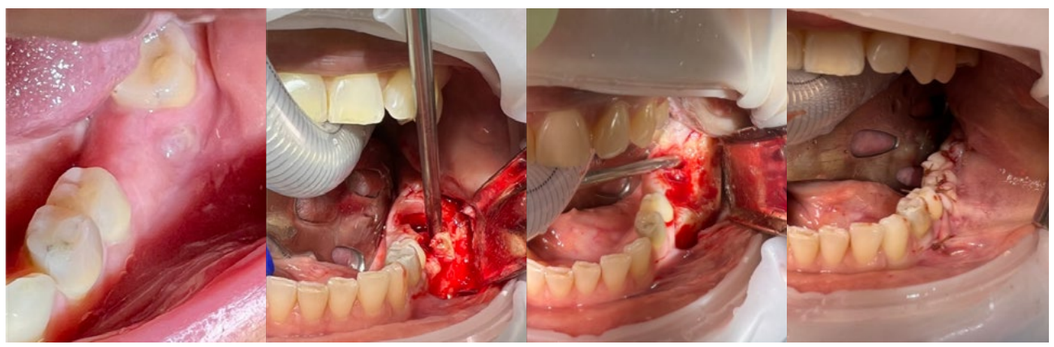
Medication-related osteonecrosis of the jaw (MRONJ)

Medication-related osteonecrosis of the jaw (MRONJ) is a multifactorial condition where exposed bone or bone can be detected through an intraoral or extraoral fistula/e in the maxillofacial region, that persists for more than eight weeks, and occurs in a patient who has previously or is currently receiving antiresorptive therapy alone or in combination with immune modulators or anti-angiogenic medications, with no history of head and neck radiation or metastatic disease to the jaws (Ruggeiro et al. 2022).

It was first reported in the dental literature in 2003 and was initially used to describe the spectrum of dental problems seen in cancer patients treated with intravenous bisphosphonates for prevention of skeletal-related events. While varying terminology such as antiresorptive-related osteonecrosis of the jaw, bisphosphonate-related osteonecrosis of the jaw, avascular necrosis of jaw, osteonecrosis of the jaw, and phossy jaw have been used, MRONJ is currently the most accepted term.

In the last two decades, there has been a steady increase in its incidence. MRONJ occurs in approximately <5% of patients with advanced cancer who are receiving a bone modifying agent (BMA), in contrast to a much smaller percentage of patients who receive BMA pharmacotherapy for osteoporosis (<0.05%) (Ruggeiro et al. 2022).

A study by Filleul et al. in 2010 reviewed 2408 cases: 88% associated with intravenous therapy (such as zoledronate and pamidronate), 11% received oral bisphosphonates, 89% had an underlying condition (multiple myeloma (43%), breast cancer (32%), prostate cancer (9%), other (5%) and 11% had osteoporosis. Of interest, 67% of these cases were preceded by tooth extraction, 7% from other factors such as ill-fitting dentures, and in 26% of cases, there was no identified predisposing factor. Other conditions in which higher rates of spontaneous necrosis may rarely occur include patients with hypercoagulable states and patients taking bisphosphonates who develop hypocalcaemia and secondary hyperparathyroidism (Landesburg et al. 2011).



57-year-old female presenting with toothache and a vital tooth 37, she was being treated with Zoledronate for metastatic breast cancer. There was no history of recent extraction and clinically she had developed bone necrosis with a draining sinus to the mandibular alveolus. The area involved the tooth 37 so it was extracted at the time of local bone debridement and a local flap was used to cover the defect. The patient went on to heal well.

MRONJ Risk in Osteoporotic Patients

The overall reported prevalence of MRONJ is between 0-0.05% (5 cases per 10,000) in patients receiving oral bisphosphonate therapy for osteoporosis, marginally higher than the incidence in the general population (0 to 0.02%) (Lo et al. 2010). Duration of oral bisphosphonate therapy for osteoporosis appears a dose-dependent risk, with increased risk after four years of oral therapy (0.21%, 21 cases per 10,000) (Lo et al. 2010), and is compounded if the patient is also being treated with long-term glucocorticoids or anti-angiogenic drugs (Ruggerio et al. 2022). A prevalence of approximately 2 cases per 10,000 (0.02%) has been reported for patients undergoing annual intravenous zoledronic therapy for three years, with no change after six years therapy. For DMB, the risk of MRONJ is reported to be of a wider range: 0.04%, four cases per 10,000, and after 10 years of follow up, 0.3 percent. The risk for MRONJ when exposed to romosozumab (0.03 percent to 0.05 percent) is comparable to alendronate (0.05 percent). Compared with patients receiving higher doses of anti-resorptives for cancer treatment, the risk of MRONJ for patients with osteoporosis exposed to anti-resorptive medications is approximately 100 times smaller.

MRONJ Risk Among Patients with Nonmalignant Bone Disease

Denosumab (DMB) can be used to manage aggressive giant cell tumours of bone. Though the literature is sparse, estimated risk of developing MRONJ is broad (0.7 percent to 5 percent). This is comparable to the risks of developing MRONJ in subjects treated with DMB for malignancies (range = 0 percent to 6.9 percent). There are very limited data describing the occurrence of MRONJ in the paediatric population for osteogenesis imperfecta and other conditions.

FIGURE 1: Nomenclature for various novel drugs

Novel drug names have four segments (and usually five syllables).

The first segment is the decision of the drug developer. The next segment is the target or disease class, to which a vowel may be added to allow pronunciation, Before 2009, tumour specific segments were used, but this practice has been discontinued because most monoclonal antibodies with oncology indications are investigated for more than one type of tumour. The third segment of the name indicates the source (eg, human, mouse) and is useful for predicting immunogenicity. The last syllable indicates the drug category.

1st Segment: Decision of Drug Developer

2nd Segment: Target or disease class
- ba (bacterial)
- li (inflammatory/immunomodulating)
- ci (cardiovascular)
- tu/-ta (tumours/neoplastic disease)
- vi (viral)
- ne (neural)
- fung (fungal)
- so/ -os (bone)

3rd Segment: Origin
- u (human)
- zu (humanized)
- o (mouse)
- xi (chimeric)
- xizu (chimeric humanized)
- l (primate)

4th Segment: Drug category
- Tyrosine kinase inhibitors (-nib)
- Mammalian target of rapamycin inhibitors (-limus)
- Variant fusion proteins (-cept)
- Monoclonal antibodies (-mab)

MRONJ Risk in Patients with Cancer

The risk of MRONJ among cancer patients exposed to zolendronate ranges between 50-100 times higher than cancer patients treated with placebo, and the cumulative incidence of MRONJ ranges from 0.7% - 6.7%). When limited to studies with Level 1 evidence, the risk of MRONJ in subjects exposed to zolendronate approximates 1% (100 cases per 10,000 patients). The risk for ONJ among cancer patients exposed to DMB is comparable to the risk of ONJ in patients exposed to zolendronate.

The pathophysiology of MRONJ is unknown. Current theories centre on 5 main ideas: inhibition of bone remodelling, infection and inflammation, a lack of immune resilience, soft tissue toxicity and altered angiogenesis. The strongest evidence supports the former two.

The diagnosis of MRONJ is primarily clinical. It is worth remembering that the requirement to have exposed bone for a diagnosis has been debated (Fedele and Porter, 2010). Other disease processes such as neoplastic infiltration of bone and osteomyelitis should be excluded. Further imaging may be required, and specialist interpretation is recommended. Radiographic features on plain film may not demonstrate early disease, however some non-specific features include increased prominence of the lamina dura around dentition, diffuse sclerosis, patchy lucencies and cortical erosions. More advanced features include sequestrum formation and periosteal reactions. The position paper of the American Association of Oral and Maxillofacial Surgeons describes a clinical staging process (Table 1). In the at-risk patient with non-specific orofacial pain, MRONJ should be considered as a differential diagnosis even if there is currently no clinically evident exposed bone in the oral cavity.

While it is well-recognised that bisphosphonates and DMB are implicated, several drugs carry the risk of this debilitating adverse effect. These include anti-angiogenic agents, monoclonal antibodies, tyrosine kinase inhibitors and variant fusion proteins, with case reports for mammalian target of rapamycin inhibitors, radiopharmaceutical Radium 233, methotrexate, prednisolone and selective estrogen receptor modulator Raloxifene. The risk appears to be higher when utilized in conjunction with bone-modulating therapies (Table 2). A study looking at the Australian database of adverse event notifications found that most cases were associated with DMB or bisphosphonates (n = 405), and there were 14 reports where secondary agents that directly or indirectly affect bone turnover, were also implicated. Some of these secondary drugs, including adalimumab, etanercept, methotrexate and rituximab have previously been associated with MRONJ in published case reports (Teoh at al. 2020).

As a guide to identifying some novel drugs, their distinct and identifying nomenclature is shown in Figure 1.

Recommendations for Drug Holidays

Bisphosphonate medications are rapidly incorporated in the bones and have an enduring effect. In contrast, DMB has a shorter half-life, and therefore the pharmocokinetics need to be considered by the treating physician and dentist when determining timing of treatment. There is conflicting evidence for the use of drug holidays, and clinicians should be aware that there is a rebound increase in bone resorption following the discontinuation of DMB, resulting in an increased risk of bone fractures. If DMB is to be suspended by the patient's medical doctor, the timing and duration of the pause in therapy should be optimised in order to minimise this risk of both MRONJ and rebound fracture.

The planned dentoalveolar surgery in osteoporosis can be completed 5 months following the last dose of DMB when the level of osteoclast inhibition is waning. It can then be reinstituted 6-8 weeks post-surgery. This timing coincides with the period of low drug activity but is prior to rebound activity of the osteoclasts.

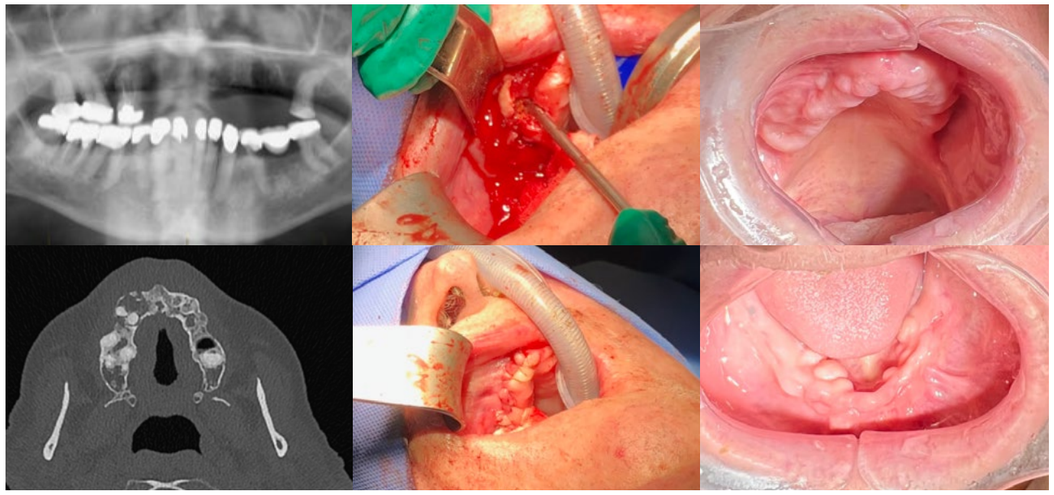
Bisphosphonates have an enduring activity on the bony tissues and pausing therapy will not directly affect the bone healing, however, emerging evidence suggests that the bisphosphonate classes have an antiangiogenic effect that inhibits mucosal healing. Many authors are recommending a pause in treatment 1 week prior to dentoalveolar surgery and recommencing 4-6 weeks after, for patients treated for osteoporosis.

Pausing drug therapy in cancer patients is at the discretion of the treating specialist physician and surgeon.

No bone turnover or other biomarkers are currently validated for estimating MRONJ risk and it is not advised to delay non-elective dentoalveolar surgery to await normalisation of bone turnover markers.

Table 1: Clinical Staging of MRONJ *(adapted from Ruggeiro et al. 2022)*

AT RISK	No apparent necrotic bone in patients who have been treated with oral or intravenous bisphosphonates or antiresorptive therapy.
STAGE 0	(nonexposed bone variant)—no clinical evidence of necrotic bone but nonspecific clinical findings, radiographic changes, and symptoms such as mobile teeth, intra or extraoral swelling, pain (may be referring to the sinus or temporomandibular joint region) and altered neurosensory function. • Radiographic Findings • Alveolar bone loss or resorption not attributable to chronic periodontal disease. • Changes to trabecular pattern sclerotic bone and no new bone in extraction sockets. • Regions of osteosclerosis involving the alveolar bone and/or the surrounding basilar bone. • Thickening/obscuring of periodontal ligament (thickening of the lamina dura, sclerosis, and decreased size of the periodontal • Alveolar bone loss or resorption not attributable to chronic periodontal disease.
STAGE 1	Exposed and necrotic bone or fistulas that probes to bone in patients who are asymptomatic and have no evidence of infection. These patients also may present with radiographic findings mentioned for Stage 0 that are localized to the alveolar bone region.
STAGE 2	Exposed and necrotic bone or fistulas that probes to bone associated with infection as evidenced by pain and erythema in the region of exposed bone with or without purulent drainage. These patients also may present with radiographic findings mentioned for Stage 0 that are localized to the alveolar bone region.
STAGE 3	Exposed and necrotic bone or a fistula that probes to bone in patients with pain, infection, and 1 of the following: exposed and necrotic bone extending beyond the region of alveolar bone (i.e, inferior border and ramus in mandible, maxillary sinus, and zygoma in maxilla) resulting in pathologic fracture, extraoral fistula, oral antral or oral nasal communication, or osteolysis extending to inferior border of the mandible or sinus floor



80 year old male patient with established stage 2 MRONJ of the maxilla with rampant dental decay requiring a full dental clearance. He was being treated with Zoledronate for osteoporosis. The Zoledronate was stopped and the teeth extracted under general anaesthesia with simultaneous debridement of the necrotic bone and local advancement flaps to close the defects primarily.

Management

MRONJ can be challenging to treat and can cause significant pain and reduced quality of life. Prevention is far preferable. Risk management when considering treating a patient who may potentially develop MRONJ necessitates informed consent with specific discussion of the patient's individual risk profile. Treatment of this condition aims to eliminate pain, control infection of soft and hard tissues and minimize progression of bony necrosis. It is largely dependent on the stage of disease and the patient's underlying medical history.

Management is often multi-disciplinary and the patient should be referred to appropriate specialists. Prevention is via reduction of modifiable risk factors (Table 3), and cornerstones include maximising patient's overall and oral health, performing high-risk surgical procedures prior to initiating therapy, using preoperative and postoperative antibiotics and antimicrobial mouth rinses, primarily closing extractions sites, and maintaining good oral hygiene. Treatment, according to the stage of the disease, may include conservative measures such as antimicrobial mouth rinses, antibiotics if clinically indicated, effective oral hygiene, and conservative surgical interventions, such as small sequestrum removal (Tsao et al. 2013). More aggressive surgical intervention may be indicated for more severe cases. There is little evidence to suggest that the use of adjunctive therapies such as hyperbaric oxygen or ozone therapy, can lead to MRONJ resolution. Other possible adjunctive therapies include Vitamin E, pentoxifylline, Teriparatide (an anabolic agent used for treatment of osteoporosis), platelet rich plasma, bone morphogenic protein, and parathyroid hormone.

Table 2: Medications implicated in MRONJ *(King at al. 2019, Teoh et al. 2020)*

Further controlled prospective studies will be required to measure the risk of MRONJ associated with non-antiresorptive agents.

DRUG CLASS	EXAMPLES	DRUG INDICATIONS
Bisphosphonates	**Oral** • Alendronate (Adronat, Fosamax) • Risedronate (Actonel) **IV** • Zoledronic acid (Aclasta)	Osteoporosis, osteopenia, Pagets Disease Bisphosphonates (BPs) are antiresorptive medica- tions that are effective in managing cancer-related con- ditions, including hypercalcemia of malignancy, spinal cord compression, and pathologic fractures (skeletal-related events [SREs]) associated with bone metastases in the context of solid tumors (such as breast, prostate, and lung cancers) and multiple myeloma.
Monoclonal antibodies	• Suffix "-mab" • Denosumab (Prolia) • Bevacizumab (Avastin) • Adalimumab (Humira) • Infliximab (Remicade) • Rituximab (Rituxan) • Romosozumab	Osteoporosis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis glucocorticoid-induced osteoporosis
Tyrosine kinase inhibitors	30 TKIs have been approved for use, 8 are implicated in ONJ. • Suffix "-nib" • Suntinib (Sutent) • Imatinib (Gleevec) • Sorafenib (Nexavar) • Pazopanib (Votrient) • Axitinib (Inlyta) • Regorafenib (Stirvarga) • Cabozantanib (Cometriq)	Hematologic malignancies such as leukaemias, renal cell carcinomas, gastrointestinal stromal tumours, soft tissue sarcomas and neuroendocrine tumours.
Mammalian target of rapamycin inhibitors	• Suffix "-limus" • Everolimus (Afinitor) • Temsirolimus (Torisel)	Renal cell cancer, neuroendocrine cancer, breast cancer, lymphoma, organ transplantation
Variant fusion proteins	• Afibercept (Zaltrap, Eylea) • Etanercept • Suffix "-cept"	Renal cell carcinoma, macular degeneration and macular edema.
Radiopharmaceuticals **Most reports have patients with previous bisphosphonate exposure.*	Radium 223 (Xofrigo	Used to localize and manage bone metastases, sometimes in combination with chemotherapy.
Disease modifying anti rheumatic drug	Methotrexate	Rheumatoid arthritis, psoriatic arthritis, Crohn's disease
Corticosteroids **2 case reports in mandible*	Predisolone	Numerous
Selective estrogen receptor modulators **Link not fully established however concerns raised.*	Raloxifene (Evista)	Breast cancer, to maintain bone density in post-menopausal women

Table 3: Some Risk Factors for MRONJ *(Ruggeiro et al. 2022)*

Duration of Antiresorptive Therapy	For DMB, the risks for developing MRONJ were 1.9 percent and 6.9 percent with <24 months and >24 months of exposure. Amongst cancer patients exposed to zoledronate, it was 1.6 percent to 4 percent after 2 years of treatment and 3.8 percent to 18 percent with more than 2 years of treatment (Ng et al). For patients receiving bisphosphonate therapy to manage osteoporosis, duration may be a risk factor but the overall risk remains low.
Dentoalveolar Operations	Most common identifiable predisposing factor. For osteoporotic patients exposed to DMB, the risk for MRONJ following tooth extraction was 1 percent. For cancer patients exposed to BPs, the risk of developing MRONJ after tooth extraction ranges from 1.6 percent to 14.8 percent. Risk of developing MRONJ after dentoalveolar operations such as dental implant placement and endodontic or periodontal procedures is unknown. Absent better data, AAOMS cautions the use of these procedures in cancer patients exposed to antiresorptive therapies and recommends osteoporosis patients be informed of low potential risks.
Anatomic Factors	MRONJ is more likely to appear in the mandible (75 percent) than the maxilla (25 percent). Denture use can be associated with an increased risk for MRONJ.
Concomitant Oral Disease	Pre-existing inflammatory dental disease such as periodontal disease or periapical pathology has been thought to be a risk factor.
Concomitant Systemic Disease	This includes cancer, conditions requiring management with corticosteroids, anaemia and diabetes.
Other Demographics	There is a higher prevalence of MRONJ in the female population and in older patients. Tobacco use is variably reported as a risk factor.

Preventive oral care methods combined with effective oral health practices are associated with a lower rate of MRONJ. It is strongly recommended that patients see a dentist prior to therapy to ensure that any teeth of questionable prognosis are assessed and extracted, if necessary, with adequate healing time. Any dental prosthesis should be well fitting in order to reduce trauma. Dental screening, prophylaxis, oral hygiene instruction, tobacco and alcohol cessation counselling, and timely treatment is recommended to reduce risk. Consensus recommendations from the American Association of Oral and Maxillofacial Surgeons (AAOMS) and the International Task Force on Osteonecrosis of the Jaw agree that elective dentoalveolar oral surgery does not appear to be contraindicated in patients undergoing anti-resorptive therapy for osteoporosis, however, identification and treatment of dental disease prior to the initiation of anti-resorptive therapy, if possible, is recommended. Patients should be adequately informed of the small risk of MRONJ.

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