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MRONJ (Medication Related Osteonecrosis of the Jaw)

Guidelines for Dental Practitioners

What is the relevance of MRONJ for Dentists?

Dental Practitioners have an important role in the prevention, diagnosis, treatment and potentially causation of MRONJ.

What is MRONJ?

MRONJ is defined 'as an area of Exposed bone or bone that can be probed through a fistula for more than 8 weeks in a patient with a history of treatment with antiresorptive (bisphosphonates, denosumab, romosozumab and/or anti-angiogenic drugs and who have never had radiotherapy or MRONJ is a rare but debilitating condition which can have a significant effect on a patient's quality of life.

What do I need to know as a Dentist treating patients at risk of developing MRONJ?

MRONJ is a rare condition with the majority (80-90%) developing in patients with malignancy (bone metastases or multiple myeloma) who are treated with frequent doses of potent antiresorptives (denosumab or zolendronic acid). In most cases (70-80%), it occurs after dentoalveolar surgery.

MRONJ in the treatment of osteoporosis is rarer but predisposing risk factors include more prolonged exposure to antiresorptives, steroid use, diabetes, smoking, poor oral hygiene, an immunocompromised state and ill-fitting dentures. Spontaneous cases may also occur, particularly in those on high doses of antiresorptives and with poor dental hygiene. The majority (75%) of cases of MRONJ occur in the lower jaw (mandible) whereas the risk appears lower in the upper jaw (maxilla).

Patients taking antiresorptive medication to help to prevent osteoporotic fractures, should be made aware that the risk of MRONJ is low, compared with the risk of osteoporotic fractures which can result in significant complications.

NOTE

1. The majority of cases (70-80%) occur after dentoalveolar surgery with tooth extractions or dental implants having the greatest risk.
2. Patients treated with denosumab appear to have a higher risk than those treated with other antiresorptives.
3. Patients with metastatic bone disease or multiple myeloma treated with frequent doses of potent antiresorptives (x 12-15 higher than in osteoporosis) and/ or antiangiogenic drugs / corticosteroids have a have a particularly high risk of MRONJ (x 100 times risk).
4. The sequential use of different antiresorptives may increase the risk of MRONJ.
5. There is no diagnostic test which can identify a patient at higher risk for MRONJ. There is some evidence that the serum bone turnover marker (C Terminal Telopeptide, CTX-1) may have a role in risk assessment prior to dentoalveolar surgery. Significant suppression of CTX may infer a higher MRONJ risk though studies have not clearly demonstrated a role for its use in guiding patient management.

6. MRONJ can rarely occur spontaneously when there is periodontal disease / periapical infection or ill-fitting dentures and with medications other than bisphosphonates.
7. A pro-active, preventive approach with regard to maintenance of good oral hygiene and treatment of dental caries in combination with patient education is the cornerstone in the prevention of MRONJ.

*The aetiology of MRONJ is complex and usually involves trauma to the jawbone followed by development of infection and ultimately impaired bone healing and necrosis. The jawbone has a high rate of bone turnover as it is subjected to significant loading forces and microtrauma on mastication. Major suppression of this bone turnover with anti-resorptive drugs may impair the normal healing response to trauma (eg dental extractions). Factors that impair bone quality (steroids), increase the risk of infection (steroids, immunocompromised state, diabetes, smoking) or affect normal healing (steroids, diabetes, anti-angiogenic drugs, smoking) all can increase the risk.

Risk of MRONJ associated with medications in the treatment of osteoporosis

	Overall (%)	**Per Tooth extraction (%)**
Oral bisphosphonates	0.01 - 0.1	0-0.3
IV bisphosphonates	0.01 -0.1	0-0.3+
Romosozumab	0.04	-
Denosumab	0.3	0- 0.68 +

Risk of MRONJ associated with medications in cancer patients

	Overall (%)	**Per Tooth extraction (%)**
Zolendronic acid	1.0	1-10+
Denosumab	0.7-.6.9	1-10+
Angiogenic medications	1.0	>1.0

*Patients with skeletal metastases or multiple myeloma have a higher risk of MRONJ than cancer patients treated for prevention of cancer therapy induced bone loss.

NB. Risk of MRONJ varies between studies due to differences in study population characteristics and drug exposure. Most report on overall incidence rate though where incidence is quoted per dental extraction / procedure it is significantly higher.

<u>Medications that increase the risk of MRONJ</u>

1. Anti-resorptive drugs used in the treatment of osteoporosis

2. Anti-resorptive drugs used to treat multiple myeloma & metastatic bone cancer

3. Anti-angiogenic drugs used as a therapy for some cancers (eg renal tumours)

4. Steroids therapy (especially high dose or long-term)

Vitamin D deficiency is associated with increased risk of MRONJ in some but not all studies. Patients on osteoporosis treatments should have a 25(OH)D level of 50 -75 nmol/l.

Bisphosphonates.

Use of bisphosphonates in the treatment of the conditions below is associated with MRONJ

- **Osteopenia or osteoporosis** (to reduce fracture risk) – oral or intravenous
- **Bone metastases from tumours or multiple myeloma** (to treat hypercalcaemia and reduce skeletal related events ie pathological fractures and spinal cord compression)
- **Adjuvant therapy in breast cancer** (intravenous)

Bisphosphonates bind to bone and have a skeletal half-life of up to 10 years: anti-resorptive effects can persist for several years meaning prior therapy may infer a risk of MRONJ. The risk of MRONJ appears to be related to the duration (cumulative dose) of exposure to the bisphosphonate. There is no clear evidence to support the use of 'drug holidays' to mitigate the risk of MRONJ.

Even historic treatment with bisphosphonates should be considered in assessing risk of MRONJ.

Bisphosphonates used in the treatment of osteoporosis

Drug	**Trade Name**	**Frequency**
Zolendronic acid (iv)	Aclasta® / Reclasta®	Once yearly
Alendronate (oral)	Romax®, Fosamax®,Fosavance®, Binosto®	Once weekly
Risedronate (oral)	Actonel®	Once weekly
Ibandronate	Bonviva®	Once monthly

Bisphosphonates used in cancer patients

Drug	**Trade name**	**Frequency**	**Indication**
Pamidronate (90 mg iv) Pamidronate (60 mg iv)	Aredia®	Once every month	Skeletal metastases Hypercalcaemia
		Once every 3-6 months	Prevention of CTBL
Zolendronic acid (4mg iv)	Aclasta®	Once every 3-6 months	Prevention of CTBL
		Once every month	Skeletal metastases Hypercalcaemia
		Once monthly	Multiple myeloma*
		Once every 3-6 months (for 2-3 years)	Adjuvant therapy in breast cancer

CTBL- Cancer Treatment Induced Bone lose eg due to aromatase inhibitors, androgen deprivation therapy.

*Once monthly for the first 12 months and frequency of therapy thereafter decided clinically.

Denosumab

Denosumab (Prolia®) is an anti-resorptive medication administered by subcutaneous injection. It is a monoclonal antibody against RANK ligand and inhibits osteoclast function resulting in profound inhibition of bone resorption. It is not incorporated into bone with its pharmacological effect wearing off after approximately six months.

•**Denosumab 60 mg (Prolia®)** administered subcutaneously every 6 months to treat osteopenia / osteoporosis or prevent bone loss in patients on aromatase inhibitors or androgen deprivation therapy.

•**Denosumab 120 mg (Xgeva®)** administered subcutaneously once monthly to treat metastatic bone disease or multiple myeloma.

Drug	Trade Name	Dosing	Indication
Denosumab (60 mg)	Prolia®	Once every 6 months	Osteoporosis
			CTBL*
Denosumab (120 mg)	Xgeva®	Once monthly	Skeletal metastases Multiple myeloma

*CTBL- Cancer Treatment Induced Bone Lose eg due to aromatase inhibitors, androgen deprivation therapy

• Denosumab use in the treatment of osteoporosis (Prolia®, 60 mg every 6 months) appears to have a higher rate of MRONJ than both oral and intravenous bisphosphonates and this may occur earlier. It also appears to infer a greater risk of MRONJ than Zolendronic acid in cancer patients.

• I**f a patient develops MRONJ on denosumab, it should not be stopped** though they should be referred to a specialist in bone health to decide on further optimal management of their osteopenia / osteoporosis**.** Many cases of MRONJ in patients on denosumab for the treatment of osteoporosis appear to heal when the drug is continued.

•**A patient should never be put on a drug holiday if on denosumab (Prolia or Xgeva) as this results in substantial bone loss and risk of vertebral fractures.** If denosumab is discontinued, it must be followed up with bisphosphonate treatment and this decision should only be made by the physician managing their osteoporosis.

3. Romosozumab (Evenity)

Romosozumab is a potent medication (with anabolic and antiresorptive effects) used in the treatment of osteoporosis / osteopenia. It has rarely been associated with MRONJ with an estimated incidence of 0.04%. It is a monoclonal antibody against sclerostin which results in both an increase in bone formation and inhibition of bone resorption. It is administered as a subcutaneous injection (prefilled pen) once monthly for 12 months. Follow up treatment is usually with an antiresorptive such as denosumab or a bisphosphonate.

NB: Romosozumab (Evenity) is approved in the EU and is currently awaiting the outcome of a cost benefit analysis by the NCPE on behalf of the HSE. Therefore, at present few if any patients are currently on treatment with Romosozumab in Ireland.

4. Antiangiogenic Medications

Antiangiogenic medications are used in the treatment of some types of cancers including colorectal, breast, lung, ovarian, kidney and liver tumours. These medications work by reducing the blood supply to the tissues and the tumour and may increase the risk of avascular bone damage and MRONJ which may occur spontaneously. Not all anti-angiogenic drugs are implicated in MRONJ but include the vascular endothelial growth factor (VEGF) inhibitors, (bevacizumab and aflibercept) and the receptor tyrosine kinase inhibitor (TKI) sunitinib.

The incidence of MRONJ in cancer patients treated with antiangiogenic medications is about 1.0% and may be greater in those on concurrent bisphosphonate and /or steroid therapy.

Antiangiogenic medications associated with MRONJ

Drug	Class	Trade name
Bevacizumab*	Anti-VEGF	Avastin®
Aflibercept*	Anti-VEGF	Zaltrap®, Eylea®
Pazopanib	Anti-VEGF	Votrient®
Cabosantinib	Anti-VEGF	Carbometyx®, Cometriq®
Erlotinib	Anti TKI	Tarceva®
Dasatinib	Anti TKI	Sprycel®
Sunitnab*	Anti TKI	Sutent®
Axitinib	Anti TKI	Inlyta®
Imatinib	Anti TKI	Gleevec®
Sorafenib	Anti TKI	Nexavar®

The relationship with other agents not marked with * is based on fewer case reports.

5. Combined Antiresorptive / Antiangiogenic Medications

Patients with multiple myeloma or metastatic bone disease may be treated with a combination of antiresorptive and anti-angiogenic medications. This combination has been associated with a greater risk of MRONJ compared with drug treatment alone. These patients are also frequently treated with steroids which may further increase this risk.

When should I suspect that a patient may have developed MRONJ?

It should be suspected in patients (treated with antiresorptive and/or angiogenic drugs) who have any of the following, especially after dento alveolar surgery:

a) jaw pain, infection and swelling of the intra-oral soft tissues
b) altered sensation, numbness, tingling (trigeminal nerve irritation)
c) loose teeth
d) delayed healing or have an area of exposed bone (may be asymptomatic)

It should be especially considered in patients at higher risk:

a) cancer patients (bone metastases, multiple myeloma)
b) patients being treated with steroids
c) IV bisphosphonate use for more than 5 years (in osteoporosis)

Diagnosis of MRONJ

MRONJ may be difficult to diagnose, particularly in the early stages,

There are four recognised stages of MRONJ (AAOMS 2014)

0 = No exposed bone but non-specific symptoms /abnormal radiology

1 = Exposed bone or fistula (no infection)

2 = Exposed bone with infection

3 = Fistula, fracture

How should I manage patients who are at risk for MRONJ?

Prevention is the cornerstone for the management of at risk patients.

- Patients who are scheduled to commence antiresorptive therapy should have a dental assessment and regular and ongoing dental care
- Consider the potential risk of MRONJ in patients presenting for regular dental reviews and especially in those who require dental treatment.
- Always update the patient's medical history and medication list prior to dental treatment. This is essential to identify at risk patients (a questionnaire is included in this guidelines pack).

The majority of patients can be managed with conservative treatment with higher cure rates in osteoporosis than cancer patients

Treatment Strategies for "At Risk" Patients

Prevention of MRONJ

- Patients should be educated on maintaining good oral hygiene and of recognising the early signs and symptoms of potential MRONJ.
- Attention should be paid to stopping smoking and optimising diabetic control especially in patients at high risk. Poorly fitting dentures and dental caries should be addressed.
- Prophylactic antibiotics before dento -alveolar surgery may reduce the risk of MRONJ and should be considered in high risk patients. Any Infection should be actively treated in advance.

Risk assessment for MRONJ

- An evaluation of risk should be made prior to dento-alveolar procedures and this assessment should factor in:

- **Medication type and cumulative exposure** with bisphosphonates
- **Indications for use** (osteoporosis versus malignancy)
- **Other risk factors** (eg steroid use, smoking)
- **Co-morbidities** (eg diabetes).

Risk assessment for MRONJ

Low risk	Osteoporosis patients treated with antiresorptives eg oral / iv bisphosphonates (< 5 years) or denosumab and not taking steroids.
Higher risk	Cancer patients treated with antiresorptives or anti-angiogenics Osteoporosis patients on antiresorptive and steroid therapy Osteoporosis patients on antiresorptives > 5 years

1. Oral bisphosphonates used to treat osteopenia / osteoporosis.

The risk of MRONJ in this patient group is very low (<1/10,000), but increases with treatment over 5 years. In many cases, patients have additional risk factors such as steroid use.

- Ideally, these patients in general should have a dental assessment prior to starting therapy and should have regular ongoing routine and preventive dental care.
- Routine dental care on treatment is recommended including periodontal treatment, dental extractions and implant placement, as the risk is low but not completely absent and an appropriate consent process around this risk is necessary.
- Bone turnover marker (CTX) may have a role in the assessment of patients prior to dentoalveolar surgery. A very high degree of suppression of CTX may increase the risk of MRONJ but no cut-off levels are established to guide this decision.

***There is no clear evidence that stopping bisphosphonates prior to treatment reduces the risk of MRONJ.** It takes about 3 months to attain the full antiresorptive effects of oral bisphosphonates and any risk of MRONJ soon after initiating therapy is negligible. Treatment with oral bisphosphonates beyond 5 yrs may be appropriate for some patients who continue to have a high risk of fracture, though thorough dental assessment and remedial work if required is advised.

2. Denosumab (Prolia) in the treatment of osteopenia / osteoporosis.

- Patients should have a dental assessment and completion of any required treatment prior to starting therapy. A preventive dental regimen should also be advised.
- If dental treatment is required on patients taking denosumab, where possible it should be carried out 5 months after the last denosumab injection (ie. one month prior to the next scheduled treatment). The bone turnover at this stage should be approaching normal. A healing period of at least 3 weeks prior to the next treatment with denosumab (Prolia) is advisable.

3. Patients <u>planned for</u> treatment with Intravenous bisphosphonates for Osteoporosis

- Patients should ideally have a dental review prior to commencing treatment and where necessary teeth should be extracted or endodontically treated followed by a period of 3 weeks healing before commencing IV bisphosphonates.

4. Patients planned for treatment Intravenous bisphosphonates (eg zolendronic acid) or denosumab for metastatic bone disease or multiple myeloma

- All these patients should ideally have all dental treatment carried out before commencing these antiresorptive therapies. Any potentially questionable teeth should be removed, or root canal treated, and a period of 3 weeks healing allowed before commencing IV bisphosphonates or denosumab.
- The role of IV bisphosphonates and denosumab in this group of patients is symptomatic and so a short delay in treatment whilst waiting for the establishment of dental health is appropriate to avoid the potential future risk of MRONJ.

NOTE: It is recommended that these patients could be managed in the same manner as those patients having radiation treatment for head and neck cancer in regard to their dental and oral care.

5. Patients being treated with intravenous bisphosphonates (Zolendronic acid) or denosumab in the treatment of metastatic bone disease or multiple myeloma

- This is a high risk group for MRONJ and so dentoalveolar surgery should be avoided unless absolutely necessary.
- Root canal treatment should be carried out in preference to extractions. However, it is important to note that in the presence of dentoalveolar infections, including periodontal disease MRONJ can occur spontaneously. The General Dental Practitioner may consider referral of these patients to a local Maxillofacial Unit of Specialist Practitioner.

6. Patients on antiresorptive medication (IV Bisphosphonates, Denosumab) combined with other immunotherapy (eg) Steroids or Chemotherapy.

- This is a high risk group for MRONJ and dentoalveolar surgery should be avoided where possible. The General Dental Practitioner may consider referral of these patients to a local Maxillofacial Unit of Specialist Practitioner.

*An example is the patient with rheumatoid arthritis on long term steroids (Corticosteroid) and an bisphosphonate.

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