NHS Education for Scotland
SDCEP Scottish Dental Clinical Effectiveness Programme

Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw

Supplement March 2024

A review of this guidance topic did not identify any evidence or other information to warrant changing the key recommendations or clinical advice in the guidance (see MRONJ Surveillance Review Report on the SDCEP website for details). Therefore, the 2017 edition of the guidance remains essentially unchanged and extant.

The review did identify newer studies reporting on medication-related osteonecrosis of the jaw (MRONJ) incidence and on drugs associated with MRONJ. Stakeholder feedback indicated that up-to-date information about these would be helpful to inform risk assessment and discussion with patients. This supplement provides recent estimates of MRONJ incidence in patients treated for cancer, osteoporosis or other conditions, and updated information on drugs that might be associated with MRONJ.

Summary

- **Reported MRONJ incidence varies widely across studies depending on factors including the condition being treated, drug type/combinations, duration of treatment, dental treatment and other risk factors.**
- **Current estimates of MRONJ incidence are typically <5% for cancer patients and <0.05% for patients with osteoporosis although the variation between studies makes it difficult to determine accurate estimates.**
- **It remains the case that the risk of MRONJ in patients taking antiresorptive and/or antiangiogenic drugs is generally small, with the risk in patients with osteoporosis significantly lower than for patients with cancer.**
- **An increasing number of drugs have been reported to be associated with MRONJ but there is currently insufficient evidence to determine estimates of MRONJ risk for these, or on which to base advice.**

MRONJ incidence

The ranges of MRONJ incidence reported vary widely depending on the indication (malignant or non-malignant conditions), drug type, dose, delivery route, duration, combination with other medications and other risk factors such as dental treatment. In addition, reported MRONJ incidence can also vary with study design, size and dental

setting. Consequently, it is difficult to determine an accurate measure of MRONJ risk. Estimates for different patient groups reported in recent position statements or systematic reviews are included in the following sections.

Cancer

The 2022 update of the AAOMS position paper on MRONJ[1] reported wide variation and a potentially higher incidence than previously for patients taking antiresorptive drugs (bisphosphonates or denosumab) for cancer, finding that most studies report rates of <5%. Recent systematic reviews provide similar estimates.[2-4] This indicates that the incidence might be higher than the approximation of 1% for cancer patients included in the SDCEP guidance, although the wide range of reported MRONJ incidence and heterogeneity between studies makes it difficult to provide an accurate estimate. Higher reported incidence could be a consequence of increased use of drug combinations in cancer therapy, longer follow up periods or improved recognition of MRONJ cases.

Although highly uncertain, the risk of MRONJ in patients taking antiangiogenics alone might be significantly lower than in patients taking antiresorptive drugs.[1,5]

Osteoporosis

The incidence of MRONJ for patients treated for osteoporosis with antiresorptive drugs has been reported as <0.05%.[1] Estimates for bisphosphonates are typically <0.05%,[1,6] while limited evidence suggests MRONJ incidence ranging from 0.04% to 0.3% in patients taking denosumab for up to 10 years.[1] These estimates are consistent with the approximation of 0.01 – 0.1% already noted in the SDCEP guidance.

Other conditions

There are limited numbers of, typically small, studies on patients with other non-malignant conditions taking bisphosphonates or denosumab, making estimates of MRONJ risk for the individual conditions very uncertain. No cases of MRONJ in children with osteogenesis imperfecta (OI) taking bisphosphonates were identified in a 2020 systematic review.[7] This is reflected in current resources from the Brittle Bone Society.[8] No recent estimates of MRONJ incidence in patients being treated for Paget's disease were identified.

Children

Although a recent systematic review includes reports of a small number of cases of MRONJ in children or adolescents treated for conditions such as giant cell bone tumour, evidence remains very limited and uncertain.[9]

Drugs associated with MRONJ

A current list of the drugs with a MHRA Safety Update for MRONJ is available on the SDCEP website and includes:

- Bisphosphonates: **alendronic acid, risedronate sodium, zoledronic acid, ibandronic acid, pamidronate sodium, sodium clodronate**;
- RANKL inhibitor: **denosumab**;
- antiangiogenic drugs: **bevacizumab, sunitinib** and **aflibercept**.

Although not subject to a MHRA Safety Update for MRONJ, increasing numbers of other drugs, including immunomodulatory agents and biological therapies, are reported in systematic reviews to be linked to cases of MRONJ.[5,10-18] However, case numbers are low, with only single cases documented to date for many of the drugs, and the evidence is of very low certainty. Consequently, there is insufficient evidence to confirm the associations or determine a quantitative estimate of MRONJ risk for these drugs.

For information, other drugs with a **possible** association with MRONJ are listed below. This list includes drugs where one or more cases of MRONJ have been reported in patients not exposed to bisphosphonates or denosumab. In many cases, however, these patients are likely to have been taking other medications and these might have contributed to the development of MRONJ.

- protein kinase inhibitors: **axitinib, cabozantinib, dasatinib, everolimus, imatinib, osimertinib, pazopanib, regorafenib, sorafenib, temsirolimus**;
- monoclonal antibodies*: **adalimumab, infliximab, ipilimumab, nivolumab, ranibizumab, rituximab, romosozumab, tocilizumab**;
- antimetabolites: **azacitidine, methotrexate**;
- tumour necrosis factor alpha inhibitor: **etanercept**.

Please note that these drugs have been identified from MRONJ cases described in recent systematic reviews and it is not an exhaustive list. Further cases may exist, and more are likely to be reported in future. In addition, be aware that when taken in combination with other drugs associated with MRONJ, including bisphosphonates or denosumab, the listed drugs might further increase the risk of MRONJ.

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* Note that not all monoclonal antibody therapies (name ending in ‘mab’) or other biologics have associations with MRONJ cases or would be expected to based on their known mechanism of action or targets.

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About this supplement

This supplement has been developed by the SDCEP Programme Development Team in consultation with members of the MRONJ Guidance Development Group.

Please refer to the MRONJ Surveillance Review Report on the SDCEP website for further details.

As with all SDCEP guidance, the information presented here does not override the individual responsibility of the health professional to make decisions appropriate to the individual patient.