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

Dental Clinical Guidance

Surveillance Review Report

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Scottish Dental
Clinical Effectiveness Programme

Contents

Review summary and guidance updating decisions

The surveillance review did not identify any new guideline recommendations or evidence of sufficient quality to warrant changing the guidance recommendations. Stakeholder feedback indicated that updated information on drugs associated with cases of MRONJ and current estimates of MRONJ incidence would be helpful.

Based on the surveillance review findings, the following were agreed:

- The 2017 SDCEP *Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw* guidance to remain extant until the next scheduled review of the topic in five years. An earlier review and updating may be triggered if any significant developments are identified prior to this.
- A separate short supplemental update to the guidance to be provided, including:
    - updated incidence data from recent sources;
    - updated information about non-antiresorptive drugs associated with cases of MRONJ, acknowledging the lack of evidence to determine a quantitative estimate of relative risk;
    - acknowledgement that there may be rare cases of MRONJ in children or adolescents;
    - information on MRONJ incidence in patients with non-malignant conditions other than osteoporosis, including osteogenesis imperfecta.
- Updated patient information reflecting current estimates of MRONJ incidence to be provided.

1 Background

SDCEP's *Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw* (MRONJ) guidance was published in 2017 as an update of the 2011 SDCEP publication *Oral Health Management of Patients Prescribed Bisphosphonates*. The guidance topic was due for further review in 2022 in line with SDCEP's five-year guidance review policy. A surveillance review was carried out to assess whether there are any developments in the area or changes in the evidence base that would impact on the guidance recommendations and inform the extent of any updating.

2 Surveillance review methods

The following steps were carried out by SDCEP to assess whether the recommendations in the guidance remain up to date.

- Guidelines used previously as sources were checked for updated versions.
- New guidelines relevant to the topic were sought by checking websites and publications of known guideline providers and relevant professional bodies including:
  - Scottish Intercollegiate Guideline Network (SIGN)
  - National Institute for Health and Care Excellence (NICE)
  - Guidelines International Network (GIN) International Guideline Library
  - ECRI Guidelines Trust
  - American Dental Association (ADA)

  and via PubMed.
- Updated and new guidelines were assessed for any changes or new recommendations that might impact on the guidance.
- A search of the Cochrane Database of Systematic Reviews and Epistemonikos, from August 2016 to November 2022, was carried out for new systematic reviews relevant to osteonecrosis of the jaw and meeting the inclusion criteria used previously for the guidance. The search was updated in October 2023.
- The conclusions of new systematic reviews were checked to assess the impact on recommendations. If the impact was unclear or the conclusions were not consistent with the guidance recommendations, the review was considered in detail.
- Information on other developments relevant to the topic were sought via a questionnaire sent to the Guidance Development Group (GDG) members.
- Feedback on the 2017 MRONJ guidance was considered (including comments sought via a survey in 2021).
- The GDG were consulted on guidance updating proposals, which were based on the assessment of the surveillance review findings (see Section 3). The 8 responding GDG members (including co-chairs) unanimously agreed to the proposals.

3 Surveillance review findings and assessment

The recommendations and clinical advice in the 2017 MRONJ guidance were based on three guidelines/position papers from professional bodies and nine systematic reviews that included evidence relating to incidence of MRONJ in various patient groups and to prevention strategies. The surveillance review identified five updated or new guidelines/position statements and more than 70 relevant systematic reviews published since the previous searches carried out in 2016 (see Appendices 1 & 2 for more information).

The significant findings from the new evidence identified, stakeholder feedback (see Appendix 3) and other developments are described in this section, with assessment of the potential impact on the guidance and proposed actions.

MRONJ incidence

- The updated and new guidelines and the majority of the new systematic reviews provide information on MRONJ incidence. The ranges of 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. Consequently, it is difficult to provide accurate estimates of MRONJ incidence.
- Summary estimates of MRONJ incidence associated with antiresorptive drugs (bisphosphonates or denosumab) from a recent AAOMS position paper[1] are <5% for cancer patients (compared to the previous estimate of 1% stated in the SDCEP guidance), and <0.05% for osteoporosis patients (previous estimate was 0.01-0.1%), although these estimates are of low certainty.
- Feedback from GDG members indicated that updated incidence data would be helpful to inform discussions with patients.

Assessment: More recent sources that include incidence data are available and updated estimates may be helpful for guidance users.

Proposal: Provide updated summary MRONJ incidence data, in a short supplemental update to the SDCEP MRONJ guidance, informed by the most recent, relevant sources and acknowledging the uncertainty in the estimates.

MRONJ risk associated with antiangiogenics and immunomodulatory drugs

- Several systematic reviews indicate that evidence on MRONJ risk with antiangiogenics alone is limited and of very low certainty, typically coming from case reports or case series.[2-6]
- There is recognition of this uncertainty in other recent sources:
  - A 2019 oncology guideline[7] advises that its recommendations for the prevention and management of MRONJ do not address antiangiogenics or other medications because of the limited evidence about these.
  - One of the criteria in the widely used definition for MRONJ from the 2014 AAOMS position paper[8] has been modified in their 2022 update[1] from 'Current or previous treatment with antiresorptive or antiangiogenic agents' to 'Current or previous treatment with

antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications'.

- The SDCEP guidance cites the 2014 AAOMS definition and includes antiresorptive or antiangiogenic drugs as risk factors for MRONJ. Therefore, in addition to patients taking antiresorptives alone or in combination with antiangiogenics, the recommendations also apply to patients who are taking antiangiogenics alone. The guidance does acknowledge that combinations of drugs may increase risk and that there is limited evidence about antiangiogenics.
- The Medicines and Healthcare products Regulatory Agency (MHRA) in the UK previously issued Drug Safety Updates identifying MRONJ as a possible adverse effect of antiangiogenic drugs, bevacizumab, aflibercept and sunitinib. The manufacturers' current Summary of Product Characteristics (SmPC) sheets for these drugs still include warnings about the risk of MRONJ.[9-11]

Assessment: There are clearly a small number of cases of MRONJ associated with antiangiogenic drugs alone, as recognised by MHRA and the drug manufacturers. Although evidence of risk is still limited, there is no new evidence to justify changing the guidance.

Proposal: Keep the recommendations applicable to patients taking antiresorptives or antiangiogenics alone in addition to those taking antiangiogenics in combination with antiresorptives.

- Feedback from guidance users and GDG members indicated that there is uncertainty about the risk of MRONJ associated with newer drugs, including biologic agents such as romosozumab, and that dental professionals would value more clarity on this.
- At least ten systematic reviews identify cases of MRONJ associated with different non-antiresorptive drugs and biological therapies.[2-6,12-16] Case numbers are small, and the evidence is of very low certainty. Higher quality studies would be required to confirm the possible associations and provide accurate estimates of risk.
- MHRA does not have Drug Safety Updates identifying MRONJ as a possible adverse effect for any non-antiresorptive drugs other than antiangiogenics bevacizumab, aflibercept and sunitinib.

Assessment: Increasing numbers of drugs are reported to be linked to cases of MRONJ, although case numbers are low.

Proposal: Provide updated information about drugs associated with cases of MRONJ, acknowledging the lack of evidence to determine a quantitative estimate of relative risk.

Other risk factors

- Recent guidelines[1,7,17] and systematic reviews[18,19] confirm that the risk of MRONJ is higher for patients with malignant diseases than for those with non-malignant conditions such as osteoporosis.
- Duration of therapy with MRONJ associated drugs, particularly in cancer patients, is still considered a risk factor in current sources.[1,7,17,20-22]

- Other potential medical and dental MRONJ risk factors reported in guidelines and systematic reviews include chemotherapy, corticosteroids, smoking, diabetes, cardiovascular disease, targeted therapies, inflammatory diseases, immunosupressants, dental extractions, dentoalveolar surgery, periodontal disease, acute dental infection, implants and oral trauma.[1,7,17,19,20,22-27] However, there is insufficient data to determine the relative MRONJ risk associated with each factor.
- Evidence of low certainty included in recent systematic reviews suggests, as previously, that intravenous drug administration and both concurrent and sequential administration of relevant medication may be associated with an increased risk of MRONJ.[2,18,28]
- Most of the systematic reviews about implants identified report that there is insufficient evidence to reliably assess the associated risk of MRONJ.[29-38]
- The guidelines and position papers that include specific recommendations about implants, acknowledge the lack of robust evidence but advise against implant placement in patients on antiresorptive therapy for cancer.[1,7]

Assessment: The current information identified about these risk factors is consistent with that already provided in the SDCEP guidance, so no change required.

Prevention and management strategies

- Recent guideline recommendations for prevention and management strategies are generally consistent with those in the SDCEP guidance.[1,7,17,20]
- A 2022 Cochrane review update[39] and two other systematic reviews[40,41] found very low certainty evidence that various preventive strategies including combinations of regular dental examinations, oral care instructions, antibiotics and specific wound closure techniques, might contribute to reducing the risk of MRONJ in cancer patients receiving antiresorptive drugs.
- Some sources acknowledge that evidence in support of prophylactic antibiotics is lacking or inconclusive,[7,42] while others recommend perioperative antibiotics for patients at risk of MRONJ.[17,41] The only study cited in support of prophylactic antibiotics that assesses antibiotics without other preventive interventions and includes a control group,[43] is a small observational study at moderate risk of bias, already considered during the development of the guidance.

Assessment: The SDCEP guidance recommends that antibiotics should not be prescribed specifically for MRONJ prophylaxis, because of insufficient evidence of effectiveness and the potential harms of antibiotic use. The guidance allows for prescribing antibiotics where required for other clinical reasons. No new evidence to justify changing the recommendations on prophylactic antibiotics or other prevention and management strategies was identified.

No change to the guidance proposed.

Drug holidays and timing of dental treatment

- New guidelines[1,7,17,20] and recent systematic reviews[44-47] found a lack of high quality evidence on the effectiveness of interrupting antiresorptive drug therapy to reduce MRONJ risk.

- The AAOMS Position Statement[1] includes advice about the timing of dentoalveolar surgery between 6 monthly doses of denosumab. Similar advice is provided in the SDCEP guidance.

Assessment: This is consistent with SDCEP advice. No change required.

MRONJ in children

- Two recent systematic reviews investigating bisphosphonate-related osteonecrosis of the jaw in children did not identify any reported cases.[48,49] Another reported 14 cases of MRONJ in children or adolescents, although only one of these cases, a patient treated with high dose denosumab for giant cell bone tumour, appears to meet AAOMS diagnostic criteria for MRONJ.[50]

Assessment: It remains the case that there is very limited evidence on MRONJ in children. This is consistent with the information already provided in the guidance.

Proposal: No change to the guidance required but could acknowledge that there may be rare cases of MRONJ in children or adolescents in the proposed supplemental update to the SDCEP MRONJ guidance.

Other developments

- Feedback from a survey conducted by the Brittle Bone Society (BBS) indicated that people with osteogenesis imperfecta (OI) being treated with bisphosphonates can experience inconsistency in their dental care. Some patients reported issues including difficulties accessing treatment, not being appropriately referred, and some dentists not knowing about or understanding their condition and lacking confidence to treat them.
- The BBS provide factsheets for people with OI about bisphosphonates and dental care.

Assessment: People with OI receiving bisphosphonates are already included in the SDCEP guidance (under non-malignant bone disease). The management of other oral health complications for this group is outwith the scope of the guidance.

Proposal: Include information on MRONJ incidence in patients with OI in the supplemental update and add a link to the BBS in the updated patient information, to try to raise awareness of the relevance of the SDCEP guidance and implications for people with OI with dental practitioners and patients.

Sustainability

- The MRONJ guidance aims to support the provision of routine dental care for patients at risk of MRONJ within primary care. This could contribute to sustainability by reducing the need for patient travel to secondary care settings which might require travelling longer distances.
- Although some of the recommendations might result in additional dental appointments, particularly at the initial management stage, this is considered necessary for effective care for this patient group.
- No other sustainability considerations specific to this guidance were identified through the surveillance review.

Appendix 1 Details of updated and new guidelines

Three guidelines from professional groups were used to inform the 2017 SDCEP MRONJ guidance; an American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper,[8] an International ONJ Taskforce systematic review and international consensus,[51] and an American Dental Association Council on Scientific Affairs summary of recommendations.[52]

AAOMS published an updated version of their 2014 position paper in 2022.[1] No updates of the other guidelines were found. A recent Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology/American Society of Clinical Oncology (MASCC/ISOO/ASCO) guideline,[7] a Korean position statement,[20] an expert group consensus paper[17] and an update to a SIGN guideline were also identified.[53] Details of these are provided below.

AAOMS Position Paper on Medication Related Osteonecrosis of the Jaws—2022 Update

As for the 2014 position paper, the 2022 update is not a systematic review but includes: an overview of the literature; a definition of the disease; risk factors; and recommendations for prevention and treatment of the condition.[1] The recommendations are based on a narrative review of the evidence although no details of the evidence searches, or appraisal are provided. However, the previous 2014 Position Paper is highly cited in the literature, so the update is also likely to be considered an authoritative source.

The most relevant changes for the SDCEP guidance are an updated definition, estimates of incidence, risk factors and prevention strategies for patients before or while taking antiresorptive drugs.

Updated MRONJ case definition:
One of the case definition criteria has been amended from:
'Current or previous treatment with antiresorptive or antiangiogenic agents'
to
'Current or previous treatment with antiresorptive therapy alone or in combination with immune modulators or antiangiogenic medications'.
This reflects the authors' judgement that the evidence of risk for drugs other than antiresorptives, including antiangiogenics, is less certain because of the small number of cases and study quality.

MRONJ incidence:
The estimates of incidence of MRONJ for patients taking antiresorptive drugs for cancer or osteoporosis have been updated to reflect more recent evidence. The upper limits of the ranges of incidence reported across studies are higher than previously, particularly for cancer patients exposed to bisphosphonates or denosumab.

The position paper concludes: 'The data suggest that antiresorptive medications are associated with an increased risk for developing MRONJ. The risk of MRONJ is considerably higher in the malignancy group (<5%) than in the osteoporosis group (<0.05%). Current data are insufficient to identify other medications as risk factors for developing MRONJ.'

Risk factors:
The 2022 AAOMS position paper lists duration of drug therapy, dentoalveolar surgery, anatomic

factors (including denture use), concomitant oral disease (e.g. periodontal disease), chemotherapy and corticosteroid exposure as risk factors. Age, sex, cancer type, comorbid conditions (e.g. anaemia and diabetes) and tobacco use are also variably reported as risk factors. These risk factors are unchanged since the 2014 version.

MRONJ prevention strategies:
Although the focus in the AAOMS update is on antiresorptive drugs, rather than antiangiogenics, the recommended prevention strategies are essentially unchanged and are still consistent with the key recommendations in the SDCEP guidance. No recommendations are made about the prophylactic use of antibiotics and the guideline advises that drug holidays are controversial.

SIGN 142: Management of osteoporosis and the prevention of fragility fractures. A national clinical guideline, updated 2021

This 2015 SIGN guideline was updated in 2021.[53] Although primarily about the medical management of patients with osteoporosis, it includes a recommendation about dental care: 'Good oral hygiene is recommended during bisphosphonate therapy and patients starting bisphosphonates should be advised to have a dental check up as soon as possible.' This is consistent with the SDCEP guidance and would not impact on its current recommendations.

Medication Related Osteonecrosis of the Jaw - Position Statement of the Korean Society for Bone and Mineral Research and the Korean Association of Oral and Maxillofacial Surgeons

This 2021 position statement includes recommendations for the management of patients who are taking bisphosphonates or denosumab for osteoporosis.[20] Although evidence sources are cited, no search information or other methodology explaining how the evidence was identified or appraised are provided.

Most of the recommendations are consistent with those provided in the SDCEP guidance. Despite acknowledging the lack of clear evidence, the position statement recommends drug holidays before dental treatment for patients taking long-term bisphosphonates or with concomitant risk factors. However, the statement cites the 2014 AAOMS position paper - the 2022 AAOMS update now advises that drug holidays are controversial and does not make a recommendation.

Therapeutic approach and management algorithms in medication-related osteonecrosis of the jaw (MONJ): recommendations of a multidisciplinary group of experts.

This consensus paper provides recommendations for the prevention, diagnosis and treatment of MRONJ in patients who receive antiresorptive drugs in the context of osteoporosis or oncologic treatment.[17] Members of the multidisciplinary expert group carried out individual literature reviews and developed the recommendations via a consensus process.

The recommended strategies for MRONJ prevention are consistent with the recommendations and advice provided in the SDCEP guidance, except for the use of prophylactic antibiotics. The use of antibiotics before, during and after tooth extractions or other oral surgical procedures is recommended in this consensus paper. However, the studies cited either do not report comparing antibiotic prophylaxis with a control or do not provide evidence to support this advice.

Appendix 1 Guideline details

Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline

This guideline, published in 2019, provides recommendations for the prevention and management of MRONJ in patients with cancer taking bone modifying agents (BMAs i.e. bisphosphonates and denosumab) for oncologic indications.[7] The guideline does not include BMAs for osteoporosis or MRONJ due to medications other than BMAs.

The guideline development involved a systematic review of the literature although due to the low volume of high-quality evidence, most of the recommendations are based on consensus of a multidisciplinary expert panel. Details of the searches and inclusion/exclusion criteria are provided. Formal quality assessment of included studies was not conducted, but informal assessment suggested that the overall quality of evidence was low. The basis of each recommendation is explained with reference to the relevant evidence and/or consensus process.

The most relevant recommendations are those relating to reducing the risk of MRONJ in patients with cancer, including: undertaking a comprehensive oral care assessment prior to initiating therapy, and implementing a care plan in coordination with the oncologist; addressing modifiable risk factors; avoiding elective dentoalveolar surgical procedures; scheduled follow up of healing; only interrupting BMAs at the discretion of the treating physician. These recommendations are broadly consistent with the recommendations and advice in the SDCEP guidance.

The guideline notes that there is insufficient evidence to recommend whether BMAs should be discontinued before dentoalveolar surgery, and that evidence about the prophylactic use of antibiotics is inconclusive.

Appendix 2 Details of new systematic reviews of evidence

The surveillance review identified more than 70 relevant systematic reviews published since the searches carried out in 2016. Most investigated MRONJ incidence in various patient groups. Three systematic reviews, including a Cochrane review, addressed MRONJ prevention strategies, with another specifically focussing on prophylactic antibiotics. Four investigated the effectiveness of drug holidays on reducing risk and ten assessed the risk associated with implants. Details of the systematic reviews are provided below.

Incidence

At least 60 systematic reviews reporting MRONJ incidence have been published since 2016. The reviews include incidence data for a range of patient groups, with variability in the treatment indication, drug type, duration, drug combinations or dental procedures considered and there is also significant overlap in the studies included, making it difficult to extract accurate summary estimates of incidence.

MRONJ risk associated with antiangiogenics and immunomodulatory drugs

Ten systematic reviews that specifically considered the risk of MRONJ associated with non-antiresorptive drugs were identified.

The most recent, France et al. identified four cases of MRONJ associated with biologics rituximab, tocilizumab or infliximab in patients treated for conditions other than cancer.[16]

Suryani et al. reported a significant association between MRONJ and non-antiresorptive therapies, with corticosteroids and chemotherapy having the highest effect size.[12] Another recent meta-analysis reported that the weighted prevalence of MRONJ ranged from 0-3% for antiangiogenics alone compared with 1-11% for antiresorptives alone.[2] These reviews noted heterogeneity in the included studies and that evidence is limited and of low quality.

Three systematic reviews focussed on cases of MRONJ associated with antiangiogenics or other drugs, in antiresorptive naïve patients.[3,4,6] Forty-two cases, from case reports, case series and unpublished medical records were reported in a recent review that included any type of non-antiresorptive cancer medication.[4] These cases were related to a wide variety of drugs and biological therapies, including angiogenesis inhibitors, tyrosine kinase inhibitors, inhibitors of mammalian target of rapamycin, BRAF inhibitors, immune checkpoint inhibitors, and cytotoxic chemotherapy agents. Inhibitors of angiogenesis were the most commonly reported association and some of the drugs have only been linked to a single case of MRONJ to date.[3,4,6] Another review identified five cases of MRONJ in patients treated exclusively with antiangiogenic, sunitinib, but found that the majority of cases associated with this drug were in patients also receiving bisphosphonates.[5]

Two other systematic reviews reported a total of five cases of MRONJ attributed solely to TNF-α inhibitors, which are used as immunomodulators to manage inflammatory conditions such as Crohn's disease and rheumatoid arthritis.[13,14] Fourteen cases of MRONJ have been linked to methotrexate therapy, also used as an immunosuppressant, although approximately half were also receiving bisphosphonates and/or steroid treatment.[15]

Appendix 2 Systematic review details

The evidence on association of MRONJ with the various non-antiresorptive drugs typically comes from very small numbers of patients described in case reports or case series, which are likely to be at a high risk of bias and consequently the evidence is of very low certainty. The systematic reviews report that the evidence is very limited and that higher quality studies are required to confirm the possible associations and provide accurate estimates of risk.

Other risk factors

Medical and dental risk factors

McGowan et al. identified 4106 cases of MRONJ from 219 studies to determine risk factors for the condition.[19] The majority of cases (72.5%) were in patients with cancer. No quantitative analysis was conducted due to significant heterogeneity between the studies. Instead, the data indicated the trends in reporting of risk factors associated with MRONJ. The most reported dental risk factor was tooth extraction, followed by periodontal disease, while chemotherapy, corticosteroids and smoking were the most frequently reported medical risk factors. Other potential MRONJ risk factors included diabetes, cardiovascular disease, targeted therapies, inflammatory diseases, acute dental infection, implants and dental trauma. The authors reported that there was insufficient data to determine the relative significance of each risk factor.

Four other systematic reviews found low quality evidence in support of extractions,[23-25,27] as a dental risk factor for MRONJ and another identified a single case of MRONJ associated with orthodontic treatment.[54] A further review reported an increase in prevalence of periodontal disease associated with MRONJ, although the direction of the association could not be determined.[26]

A meta-analysis of nine case-control and cohort studies found a significantly higher risk of malignant disease in patients with MRONJ compared to those also taking antiresorptive or antiangiogenic drugs but without MRONJ (RR: 2.62; 95% CI: 1.58–4.33; P=0.0002; n=1316).[18] Sub-group analysis indicated an association between intravenous drug administration and MRONJ (RR: 2.67; 95% CI: 1.27–5.58; P=0.009; n=844), but did not demonstrate a statistically significant influence of chemotherapy on MRONJ occurrence (RR: 1.64; 95% CI: 0.79–3.39; P=0.18; n=458).

A systematic review of patients treated with antiresorptive drugs for osteoporosis found that corticosteroids and immunosuppressants were the most commonly reported concomitant medications in MRONJ cases.[25] A review investigating MRONJ in non-oncologic immunocompromised patients concluded that there was insufficient high quality evidence to quantitatively determine the risk for this patient group.[55]

MRONJ drug combinations

Meta-analysis in two systematic reviews suggests that both concurrent and sequential administration of relevant medication may be associated with an increased risk of MRONJ. The relative risk of MRONJ with concurrent antiangiogenic and antiresorptive drug treatment was 2.57 times as high as with antiresorptive drugs only (95% CI: 0.84–7.87; not statistically significant) and 23.74 times as high as with antiangiogenics only (95% CI: 3.71–151.92).[2] Pooled weighted prevalence of MRONJ associated with antiresorptive drugs was reported as 19% (95% CI 10–27%) for sequential pamidronate-zoledronate therapy, 10% (95% CI 3–22%) for sequential ibandronate-zoledronate therapy, 13% (95% CI 3–22%) for sequential bisphosphonate-denosumab therapy

while for bisphosphonates only was 5% (95% CI 0–9%) and denosumab only was 4% (95% CI 3–5%).[28] Both reviews noted methodological limitations and statistical heterogeneity in the included studies.

MRONJ drug duration

A systematic review of the long term benefits and risks of bone modifying agents in patients with breast or prostate cancer reported incidences of MRONJ ranging from 1-4% in the first two years to 3.8-18% after two years for bisphosphonates, and 1.6% in the first 2 years to 6.9% after two years for denosumab.[21]

Dosing frequency

Meta-analysis of patients with breast cancer receiving intravenous bisphosphonates did not find a significant difference in MRONJ risk comparing 4 weekly with 12 weekly doses (RR = 0.82; 95% CI 0.15–4.53).[56]

Implants

Ten systematic reviews that investigated the risk of MRONJ associated with implant placement were identified.[29-38] No relevant randomised controlled trials (RCTs) were found and the majority of MRONJ cases came from case series, which provide the lowest level of evidence. Consequently, most of the reviews reported that there was insufficient evidence to reliably assess the risk associated with implants. Despite this, it appears to be widely agreed that implant placement should be avoided in cancer patients treated with antiresorptive drugs.

Prevention

A 2022 Cochrane review update assessed the effectiveness of interventions for the prophylaxis of MRONJ, considering evidence from five RCTs.[39] One small RCT, of men receiving intravenous bisphosphonate for metastatic prostate cancer, provided very low-certainty evidence that dental examinations at three-month intervals and preventive treatments (including prophylactic antibiotics and specific wound closure techniques) was more effective at reducing MRONJ cases than standard treatment (RR 0.10, 95% CI 0.02 to 0.39; 253 participants). The different parts of the intervention were not tested individually so it was not possible to identify which contributed most to the effect seen. There was insufficient evidence from the other RCTs to conclude whether other preventive interventions investigated would reduce the risk of MRONJ.

Karna et al. similarly investigated the effectiveness of preventive dental interventions for reducing the risk of MRONJ in cancer patients receiving antiresorptive therapy but included evidence from controlled clinical trials, case-control and cohort studies in addition to RCTs.[40] The preventive measures used in the six studies included baseline check-ups, oral care instructions, dental treatment before initiating antiresorptives and plasma-rich in growth factors. Although, overall, the measures decreased MRONJ incidence by 77.3% (95% CI=47.4–90.2%; p=0.001; 2332 participants), the quality of the evidence was low due to high or unclear risk of bias. Furthermore, the preventive measures varied between studies but were combined in the meta-analysis, so no conclusions can be drawn about the effectiveness of the individual strategies.

An earlier systematic review included 15 observational studies (mostly case series with a high risk of bias) in a qualitative analysis of improved oral hygiene, antibiotic prophylaxis, and altered surgical techniques or new approaches for MRONJ prevention.[41] Based on these studies, the

authors recommend pre-therapy dental examination and oral hygiene measures, and antibiotic therapy. Only one of the four studies on antibiotic prophylaxis assessed antibiotics separately from other interventions and included a control group.[43] This small, low certainty study was considered previously during development of the SDCEP guidance.

Antibiotics

A 2021 systematic review focussing on prophylactic antibiotics assessed whether their administration could decrease the risk of MRONJ after extractions in patients taking antiresorptive drugs.[42] Only observational studies were found, most of which used other preventive strategies at the same time and/or did not have a control group. Only one small retrospective study[43] (also included in Poxleitner et al.) compared dental surgical procedures with or without antibiotic prophylaxis. Although there were more cases of MRONJ in the group who did not receive antibiotics, the study had a small sample size and other moderate to high risks of bias. The review authors reported that the evidence for prophylactic antibiotics to reduce the incidence of MRONJ after extractions is inconclusive.

Drug holidays

A recent systematic review and meta-analysis found no significant effect of antiresorptive drug holidays on MRONJ incidence after tooth extraction, although the evidence analysed was of very low certainty.[47] Similarly, a systematic review investigating whether temporary discontinuation of high dose antiresorptive drugs in cancer patients at the time of dental surgery reduces MRONJ development concluded that there was a lack of high level evidence for the use of drug holidays.[44] Two systematic reviews assessing long term osteoporosis treatment, although focussing on fracture prevention rather than MRONJ after invasive dental treatment, also found that evidence on drug holidays was limited. [45,46]

MRONJ in children

The 2017 SDCEP guidance reported that no cases of bisphosphonate-related osteonecrosis of the jaw in children had been identified. Two systematic reviews published in 2020 also did not identify any reported cases.[48,49] A recent systematic review reported 14 cases of MRONJ in children or adolescents being treated for thalassemia major, giant cell granuloma of the jaw or giant cell bone tumour.[50] However, in all but one of the cases it is unclear what diagnostic criteria for MRONJ were used.

Appendix 3 Stakeholder feedback

Dental practitioner survey

A survey of primary care dental practitioners was conducted by SDCEP's partner programme, Translation Research in a Dental Setting (TRiaDS), in 2021 (completed January 2022).

- 157 respondents.
- Almost all respondents were aware of the SDCEP MRONJ guidance.
- Approximately 97% of respondents considered the guidance to be useful, with over two-thirds rating it as extremely useful.
- Various free text responses about guidance amendments were provided in which the most common theme was a request to update the list of drugs associated with MRONJ.
- Other themes included: improved communication with patients about the long-term nature of the effects of certain drugs; improved communication between GMPs and dentists.

GDG questionnaire

A questionnaire seeking feedback received about the MRONJ guidance and information on relevant developments in the topic area was sent to members of the Guidance Development Group (GDG) in October 2022.

- Ten GDG members provided responses.
- Responses indicated that feedback received from users was predominantly positive with most colleagues finding the guidance very useful to refer to and use for patients.
- The increased range of drugs potentially associated with MRONJ risk, including the new antiresorptive romosozumab, was noted.
- Updated MRONJ incidence data was requested, to inform communications about risks with patients.
- A need for clarification around the MRONJ risk with biologic medications was reported.
- No concerns about the guidance recommendations were identified.

Patient feedback

A survey was conducted by the Brittle Bone Society on the experiences of dental care for people with osteogenesis imperfecta. Reported issues included:

- Difficulty accessing dental treatment in primary or secondary care.
- Dentists lacking experience or confidence for providing treatment for patients with osteogenesis imperfecta.
- Dentists lacking experience or confidence for providing treatment due to the patient's current or previous bisphosphonate therapy.

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