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The issue with incidence: a scoping review of reported medication-related osteonecrosis of the jaws (MRONJ) incidence around the globe

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ABSTRACT

Background Medication-related osteonecrosis of the jaws (MRONJ) can be a debilitating condition which is challenging to manage. While vast literature exists surrounding MRONJ, many studies have small participant numbers and are heterogeneous in design, leaving unanswered questions and making evidence-based practice challenging.

Objective Provide an overview of recent MRONJ incidence data, over a 5-year period, identify potential issues in reporting MRONJ cases and propose changes for future reporting.

Eligibility criteria Studies with original data regarding MRONJ incidence published from 2015 to 2020.

Sources of evidence A search was conducted on MEDLINE Ovid, the National Library of Medicine's bibliographic database, using a combination of medical subject headings (MeSH) and free text terms and run on 29 April 2021.

Charting method Each title was hand-screened, and the abstract/article in full was reviewed to establish suitability for inclusion by two authors. Data extraction by two reviewers included author, year of publication, study design, population—cancer/osteoporosis/both/other, description of population, sampling method, exclusion criteria, single centre Y/N, reported rate of MRONJ cases/number of participants, details of diagnosis and diagnostic criteria, duration of follow-up and location of study.

Results The initial search returned 1186 titles, detailed screening and inclusion of additions resulted in 92 articles for data extraction. Mean incidence of MRONJ across all studies was 4.34% (median 2.42%, range 0% to 31.80%). The mean incidence based on patient group was oncology 6.22% (32 954 participants), osteoporosis 0.58% (498 443 participants), oncology and osteoporosis 7.21% (54 7651 participants) and other, including autoimmune, inflammatory and other bone conditions, 2.55% (4487 participants). Further analysis showed incidence influenced by study size (>500 participants), diagnostic criteria used, location of study and other factors.

Conclusion Heterogeneity in studies reporting MRONJ incidence impacts results and conclusions. Standardised, contemporaneous reporting of MRONJ cases would eliminate this variation and provide valuable insight into the epidemiology, natural history and outcomes of these patients, supporting evidence-based management and service provision of patients affected.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Gaps in the medication-related osteonecrosis of the jaws (MRONJ) knowledge and research may reduce confidence in clinicians managing the condition and raise uncertainty among patients affected by MRONJ.

WHAT THIS STUDY ADDS

⇒ An overview of recent international MRONJ incidence data highlighting the challenges associated with the collection and reporting of such data.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Increasing knowledge base, informing prescribers and at-risk patients, enables evidence-based decision-making and may facilitate the planning of services and future research.

INTRODUCTION

Rationale

Medication-related osteonecrosis of the jaws (MRONJ) is a potentially debilitating and notoriously difficult condition to manage with huge implications for patients and clinical staff. Osteonecrosis of the jaws (ONJ) related to medications was first reported in 2003 by Marx as he noted patients presenting with areas of necrotic and painful exposed bone in their jaws with a history of prescribed antiresorptive medications.[1] Since 2003, the link between bisphosphonates and ONJ has been clearly recognised, with additional medications also being implicated, such as antiangiogenics and other immunomodulatory medications; this list of medications is ever-changing.[2] As a result, the nomenclature of the condition has evolved

from bisphosphonate-related osteonecrosis of the jaws to become the current term MRONJ.[2] In 2007, the first American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper on ONJ was published detailing classification, guidance on treatment, risk factors and incidence data.[3] This document is periodically revised due to the evolving picture of the condition, most recently updated in 2022.[4]

Definition of MRONJ

For patients to be diagnosed with MRONJ as per AAOMS guidance, they must satisfy all the following characteristics:[2 4]

- "Current or previous treatment with antiresorptive therapy alone or in combination with immune *modulators or antiangiogenic medications*.
- Exposed bone or bone that can be probed through an intraoral or extraoral fistula in the maxillofacial region that has persisted for longer than 8 weeks
- No history of radiation therapy to the jaws or obvious metastatic disease to the jaws".[2]

MRONJ can significantly affect patients' quality of life with symptoms such as pain, infection and even fractured jaws.[5] It can occur spontaneously or be precipitated by dental extractions, poor-fitting dentures or periodontal treatment.[4 6] MRONJ can also lead to interruption of the patient's vital medications as they may be stopped with the development of MRONJ.

While AAOMS provides an excellent review of the epidemiology, risk factors, and management strategies based on staging, the recommendations lack specificity, and there are well-reported gaps in knowledge leading to uncertainty among clinicians on how to manage the condition.[6] General Dental Practitioners also report a lack of confidence in managing at-risk patients due to a lack of data and guidance, which may result in increased unnecessary referrals to secondary care.[7] This highlights additional areas of much-needed further research.

MRONJ is generally considered to be rare; however, reported incidence rates in literature are largely estimated due to acknowledged difficulties in MRONJ research, such as small patient numbers, heterogeneity in studies and multiple variables thought to influence MRONJ development. Therefore, true incidence rates have yet to be ascertained, echoed in both the AAOMS position paper 2022 and by the Scottish Dental Clinical Effectiveness Programme (SDCEP), a leading body on evidence-based management of clinical issues in dentistry, with a statement on the need for increased epidemiological data in this area.[4 8] Without true incidence data, we cannot confidently provide patients with evidence relating to risk when prescribing these medications or undertaking procedures at risk of causing MRONJ. We furthermore cannot ensure resources are correctly allocated in services to meet population needs with clear implications for patient care and utilisation of services.

Objective

Provide an overview of recent international epidemiological data, over a 5-year period (2015-2020), ascertain more information on the scale of the issue, identify potential issues involved in MRONJ reporting and propose changes for data gathering to aid harmonisation of information.

Research question

What is the incidence of MRONJ in patients receiving anti-resorptive, anti-angiogenic medications or other drugs implicated in MRONJ development either alone or in combination?

The research question was further defined according to population, concept and context:

Population—adults or children at risk of developing MRONJ due to prescription of implicated medication.

Concept—incidence of MRONJ development.

Context—published literature with original MRONJ incidence data over a 5-year period; any treatment setting or geographical location.

METHOD

Protocol

Protocol was developed using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Scoping Review Extension; it was not submitted for publication. All details involved in the protocol are included in the article.

Eligibility criteria

Inclusion criteria: a broad range of study designs containing incidence data on MRONJ were included, covering both observational (eg, cohort studies, case series and datasets) and experimental studies (eg, randomised and non-randomised clinical trials). Where systematic reviews were identified, the primary studies within each review were screened to ensure there was no duplication of data within the scoping review. Studies on both adults and paediatric populations were included. The search included all medications that at the time were linked with MRONJ (including antiresorptive medications, antiangiogenic medications and other immunomodulatory medications).

Exclusion criteria: non-human studies, non-English articles that could not be translated, non-full articles except those where all data to be extracted were included in the summary/truncated version, duplications, case reports and conference abstracts.

Search and information sources

A search was conducted on MEDLINE Ovid using both MeSH and free text terms to reflect the nature of the research question, as illustrated in online supplemental appendix 1. The search was run on 29th of April 2021 to capture studies with published MRONJ incidence data from 2015 to 2020. The aim of this study was to provide a snapshot of the epidemiology picture over a recent 5-year

period. A pragmatic approach was taken regarding the time period; it was chosen to allow the capture of a large amount of data, providing an overview of the condition. The authors felt a shorter period may have been restrictive, and a longer time frame may have become unmanageable in terms of the number of papers returned. Given the large number of titles returned in the search, it was judged that any additional benefit from updating the search was perhaps minimal at this stage.

Selection of sources of information

Screening was conducted independently and in duplicate (ASEC and A-MG). Where it was unclear from titles alone whether the studies were suitable for inclusion, the abstract or the article in full was reviewed to establish suitability for inclusion. Any disagreements were to be discussed in full and, if agreement could not be reached, to be settled by an impartial third party. In this review, discussion was not required for any disagreements. Reference lists of all included studies were also hand-searched for additional studies.

Data charting process

Data extraction was carried out by the reviewers and input into an Excel spreadsheet.

Data items

Extracted data included:

- Author, year of publication and study design
- Population—cancer/osteoporosis/other
- Description of the population, including medication involved in the study
- Sampling method
- Exclusion criteria
- Single centre Y/N
- Reported rate of MRONJ cases/number of participants
- Details of who undertook the diagnosis—patient-reported, dentist or OMFS clinician
- Diagnostic criteria—according to AAOMS classification (Y/N/not specified)
- Duration of follow-up
- Location of the study

Critical appraisal of individual sources of evidence and synthesis of results

Given the anticipated scoping nature of the review, no assessment of quality or statistical analysis, other than descriptive reporting of incidence rates, was undertaken. A narrative discussion of difficulties associated with the reporting of incidence data for MRONJ was included, highlighting aspects which may introduce bias. A formal assessment of bias was not undertaken due to heterogeneity between multiple factors included in the included studies.

RESULTS

The following results are based on the analysis of data extracted from papers included in online supplemental table 1). Full details of the raw data are presented in online supplemental table 1) alongside the associated references to all studies included in the review. The references below relate to papers directly cited in the article.

Selection of sources of evidence

The initial search returned 1186 titles to be screened. Screening of titles/abstracts resulted in 143 studies for inclusion. Five additional studies were identified through the screening of systematic reviews. A hand search of the reference lists of other studies resulted in six further studies. The detailed application of the inclusion criteria during data extraction resulted in a total of 92 full articles for inclusion in the scoping review (see online supplemental table 1 for study characteristics and details from each included study). Critical appraisal was not undertaken as above.

Results of individual sources of evidence

Study design

A mix of both experimental and observational studies was identified, with the majority being either randomised control trials (RCTs) (n=29) or cohort studies (n=21). The purpose of the included studies varied. Observational studies tended to explore the number of people developing MRONJ when prescribed a particular drug. Such studies included, for example, epidemiological database reviews, single cohorts/case series, audits of healthcare claims and analysis of locally kept databases. Experimental studies, such as randomised controlled trials, evaluated specific drugs for the management of a specific disease (eg, denosumab use in breast cancer management); within these trials, MRONJ was largely noted only as an adverse event. Other studies, such as those from oral and maxillofacial surgical units, focused on examining a specific intervention in patients at risk of MRONJ, for example, 'all those who required a dental extraction'.

Within the included studies, the sampling technique, where specified, was largely systematic sampling between two time points to collect data on all cases meeting specific inclusion criteria. However, many studies were not explicit regarding the sampling approach, making it difficult to determine whether selection bias was potentially a cause for concern or not.

There was variation in the inclusion/exclusion criteria for the identified studies, as perhaps expected, given the variation in aims of individual studies; 31 studies (34%) did not provide explicit criteria. Additionally, it was noted that some studies (n=10; 10.8%) stated the exclusion of patients with dental infections or those requiring dental treatment/extractions. This was most common in clinical trials of oncology medications.

The duration of the follow-up period of included studies was unspecified in 35 studies (38%). Several included a

Table 1 Mean reported rate of MRONJ by indication for the causative medication

	Mean reported rate of MRONJ, %	Median reported rate % (range)	Number of studies (number of participants)
Oncology	6.22	3.74 (0 to 31.80)	49 (32954)
Osteoporosis	0.58	0.12 (0 to 3.89)	24 (498443)
Oncology/osteoporosis	7.21	4.17 (0.02 to 27.60)	7 (547651)
Other	2.55	1.86 (0 to 6.20)	12 (4487)
Overall	**4.34**	**2.42 (0 to 31.80)**	**92 (1083535)**

MRONJ, medication-related osteonecrosis of the jaws.

follow-up period with a lower limit of <3 months (n=8); most studies, however, included a follow-up period of over 1 year (n=46; 52%) (see online supplemental table 1). It should be noted that the definition of follow-up period varied across studies and study designs. In some, follow-up referred to the duration of time on antiresorptive agents, particularly in observational studies. Others referred to the period of follow-up after the end of an experimental treatment period, typically in RCTs, particularly in some of the larger extension RCTs.

Within the review, study populations were grouped together based on the indication of medication implicated with MRONJ (table 1). This categorises patients into those prescribed medications for the management or prevention of osteoporosis, as part of oncology treatment or for treatment of other conditions. In oncology studies, a range of malignant conditions were covered, including prostate cancer, renal cell carcinoma, breast cancer, bladder cancer, multiple myeloma and various metastatic diseases. The studies reporting on conditions other than osteoporosis or cancer included patients with bone diseases (fibrous dysplasia, osteogenesis imperfecta and Paget's disease), giant cell tumours and inflammatory conditions such as inflammatory bowel disease. The grouping of patients based on bony conditions such as osteoporosis and/or oncology indications is common across MRONJ literature. The grouping of 'other' is less common due to the smaller number of publications. It was felt important to include the 'Other' conditions to provide a comprehensive overview of incidence rates (table 1). The mean incidence of MRONJ across all studies was 4.34% (median 2.42%, range 0% to 31.80%).

Table 1 shows studies with participants prescribed antiresorptive medications for oncology reasons had the highest mean incidence rate, 6.22%. This group included the largest number of studies (n=49), with 32954 participants. The osteoporosis group included the highest number of participants; 498443 from 24 studies and the lowest mean incidence at 0.58%. It should be noted, the studies including both osteoporosis and oncology patients reported a mean incidence of 7.21%, higher than either the oncology or osteoporosis groups individually. The 'Other' group, including conditions such as fibrous dysplasia, giant cell lesions, inflammatory bowel disease, osteogenesis imperfecta, Paget's disease and other autoimmune conditions, had a mean incidence of 2.55%. Again, these studies are heterogeneous, reporting a wide variation in the incidence of MRONJ.

Diagnosis/diagnostic criteria

Data on MRONJ diagnostic criteria used and who undertook the diagnosis were recorded for all included studies. 62 studies did not report diagnostic criteria used. As previously described, the AAOMS diagnostic criteria are largely considered the gold standard and well used in the literature.[4] The use of AAOMS or a variation thereof was reported in 28 (30.4%) of the included studies. For many clinical trials of specific drugs, the National Cancer Institute Common Terminology Criteria for Adverse Events, V.4.0 (NCI-CTCAE V.4.0), was reported as the diagnostic criteria used, which describes ONJ in line with the AAOMS classification.[9]

While 49/92 (53%) studies did not explicitly specify who undertook the diagnosis, studies using AAOMS and NCI-CTCAE V.4.0 were assumed to have undertaken clinician diagnosis despite further clarification not included in the studies. A total of 42/92 (46%) studies were identified as having MRONJ diagnosed by a clinician (eg, dentist or oral and maxillofacial surgeon). Other studies included patients who self-reported the development of MRONJ via interview or questionnaire, which was then verified or not by clinicians.

Studies for which MRONJ was diagnosed by a clinician and/or AAOMS provide evidenced from 42 studies with 614214 participants. Interestingly, the mean incidence of MRONJ was higher in this subset of studies in comparison to incidence from all 92 included studies in the larger analysis (5.00% vs 4.30%) (see table 2). This increased incidence rate of MRONJ diagnosed by a clinician and/or AAOMS holds across all disease groupings apart from the 'other' group (2.19% for clinician diagnosed (3299 participants, five studies) versus 2.55% (4487 participants, 12 studies).

Location of study

Studies were grouped according to the continent of study (table 3). Some larger studies were

Table 2 Mean reported rate of clinician-diagnosed MRONJ by indication for the causative medication

	Mean reported rate of clinician-diagnosed MRONJ	Number of studies (number of participants)
Oncology	7.38%	20 (4501)
Osteoporosis	0.73%	13 (84 679)
Oncology/osteoporosis	9.84%	4 (521 735)
Other	2.19%	5 (3299)
Overall	**5.00%**	**42 (614 214)**

MRONJ, medication-related osteonecrosis of the jaws.

cross-continental and are therefore grouped as 'multiple'; a small number was not specified.

The largest number of studies in this 5-year period was produced in Asia (n=25) and Europe (n=34). When reviewing mean incidence based on the continent of study, studies conducted in Australia and Europe report far higher rates than all other groups (10.10% and 6.46%, respectively, vs 0.56% to 2.74% across all other locations).

Number of participants

Number of participants varied hugely across studies (range 13 to 521 695) with a mean of 11 882 participants.

If excluding studies containing 500 or fewer participants, 38 studies remain for analysis. Participant number from this group ranged from 502 to 283 586 with an average of 28 264. The mean incidence rate across all studies with more than 500 participants is 1.71% (38 studies) compared with 4.34% (92 studies). This reduction was not seen across study groups; a breakdown via group is seen below in table 4.

DISCUSSION

Summary of evidence

It is well documented that further evidence regarding MRONJ is required to support prevention, management and understanding of the natural course of this condition and facilitate evidence-based communication with patients regarding risk. Good quality data on MRONJ patients can be difficult to garner for multiple reasons. As MRONJ case numbers can be low, it is difficult to gather large amounts of data due to the sporadic presentation of these patients to clinicians. Additionally, patients often have large numbers of variables, such as multiple comorbidities, medications and complex needs, which can make the combination of data challenging. This scoping review was designed to mitigate some of these factors.

Although there is significant heterogeneity in study type, size, follow-up period and variables examined in the included studies, one of the strengths of this review is the inclusion of data from over a million participants across a large number of studies.

Population

Studies recruiting participants prescribed antiresorptive medications for oncology indications had the highest average incidence, 6.22%. This group included 49 studies with 32 954 participants. Medications associated with MRONJ for oncology indications are often given more frequently, in different modalities and in combination with other medications (eg, chemotherapy/high-dose steroids), compared with those used for osteoporosis and other conditions. It is, therefore, well reported that this patient group often has the highest average incidence.[10 11] Additionally, oncology patients can be significantly systemically unwell, with the impact on the immune system of these patients potentially contributing to compromised healing.[2 10 11]

The osteoporosis group included the highest number of participants, 498 443 from 24 studies, indicating some of the included studies were very large. Osteoporosis is an incredibly common condition; the International Osteoporosis Foundation reported in 2019 that 3.7 million people in the UK had osteoporosis[12] and first-line treatment for the management and prevention of osteoporosis is with antiresorptive drugs in many countries. Therefore, for potential data gathering purposes,

Table 3 Mean reported rate of MRONJ by continent

	Mean reported rate of MRONJ, %	Median, % (range)	Number of studies (number of participants)
Australia	10.10	2.70 (0 to 27.60)	3 (1475)
Asia	2.40	1.10 (0 to 10.56)	25 (132 430)
Europe	6.46	4.87 (0 to 31.80)	34 (599 749)
South America	0.60	NA	1 (342)
North America	2.55	2.55 (0 to 20.63)	13 (320 835)
Oceania	0.56	NA	1 (535)
Multiple	2.74	2.61 (0 to 6.82)	13 (27 135)
Not specified	2.73	2.73 (0.20 to 5.26)	2 (1034)

MRONJ, medication-related osteonecrosis of the jaws.

Table 4 Mean reported rate of MRONJ by indication for the causative medication in studies with more than 500 participants

Group	Mean reported rate of MRONJ, %	Median reported rate % (range)	Number of studies (number of participants)
Oncology	3.14	2.61 (0.00 to 11.1)	15 (27 397)
Osteoporosis	0.60	0.28 (0.00 to 3.89)	18 (523 084)
Oncology and osteoporosis	0.08	0.08 (0.02 to 0.14)	2 (521 695)
Other	2.29	1.42 (3.00 to 5.26)	3 (3735)
Overall	**1.71**	**0.46 (0 to 11.10)**	**38 (1 075 911)**

MRONJ, medication-related osteonecrosis of the jaws.

patients with osteoporosis are a much larger group who may be at risk of MRONJ compared with certain cancers for example, which may account for variation in study size. The mean MRONJ incidence for the osteoporosis group was 0.58%, which is similar to previously reported rates (0%–0.40%),[2 4 13] although slightly higher than some studies. This is likely from the culmination of a large number of variables in studies within this review, including duration of medication, use of oral versus intravenous agents, comorbidities and potential MRONJ-initiating events such as dental extractions, which may form part of the exclusion criteria of single studies.

When looking at studies including both oncology and osteoporosis patients, this group contained seven studies with 547651 participants. Surprisingly, the mean incidence of MRONJ in this group was 7.21%, higher than the oncology group, 6.37%. Some of the joint studies were from oral and maxillofacial surgical papers analysing 'at risk' patients undergoing dental extractions, a known risk factor for MRONJ development, involving both oncology and osteoporosis patients. Again, some individual studies in this review excluded all patients requiring dental treatment, which may lower the rates in comparison to this combined group. An additional general note regarding exclusion criteria across the groups was the exclusion of participants with additional comorbidities, which are documented as potential contributing factors in MRONJ development, such as diabetes mellitus or steroid use, from some studies. As these factors may increase the risk of MRONJ, such exclusions may skew the results by potentially omitting cases, limiting the generalisability of the findings and introducing bias.

The 'Other' group, including multiple conditions noted above, had a mean incidence of 2.55%. This is a less frequently discussed group at risk of MRONJ, and while again these studies are heterogeneous in design and variables, this is an interesting finding. This group contains participants with multiple comorbidities, several of which are inflammatory in nature and may be treated with other drugs impacting on the immune system, such as corticosteroids, for example, which may contribute to MRONJ risk. Additionally, nine of these studies were small (<500 participants), the impact of which will be further discussed below.

Paediatric patients are suspected to have a lower incidence of MRONJ compared with an adult population. This may be related to factors including conditions managed by causative medications, medication protocols as well as underlying physiology.[14] The decision was made to include all studies (adult and paediatric) in one analysis to provide a comprehensive overview of MRONJ incidence.

Further examination based on specific medication in each study was explored; however, the variation was too great between specific drugs, modality, frequency/dosage regime and exclusions. Length of time on certain medications can also be an influencing factor in MRONJ development as well as any 'holidays' from drugs.[6 15] Therefore, further examination based on medication was omitted as not feasible in this type of analysis due to variation between influencing factors and lack of detail in included studies.

Study size

The size of the study is frequently discussed, regarding MRONJ research, posing potential issues with the robustness of findings. Common discussion points include the overinclusion/underinclusion of cases due to the low estimated incidence of MRONJ, the size of the study and the methodology of sampling. One could argue smaller studies are easier to manage, with stricter inclusion/exclusion criteria and closer to true incidence, but conversely, a small study may inadvertently not include any cases due to a small true incidence. AAOMS in 2014 advised that studies with <500 participants should be interpreted with caution,[2] as when analysing low incidence events, studies with small numbers tend to return a higher incidence rate. Additionally, publication bias might favour reporting of studies that do include MRONJ cases compared with those that do not, again resulting in higher estimates of incidence from smaller studies. By combining many different study types and sizes, we aim to mitigate some of these factors.

We further analysed study size, by removing studies with <500 participants (n=38), and noted a reduced mean MRONJ incidence as compared with all included studies (n=92), 1.70% versus 4.30%, see

table 4. This reduction in mean incidence was noted in the 'Oncology' (3.14 vs 6.22%) and 'Other' group (2.29 vs 2.55%). Osteoporosis incidences were almost identical (0.60 vs 0.58%). The 'Osteoporosis and Oncology' group was quite different, (0.08 vs 7.21%) despite both samples containing more than 500 000 participants. This is potentially because four studies in the osteoporosis/oncology group in the main analysis contained very low participant numbers (40–159) and very high incidence (4.17%–27.6%), see online supplemental table 1), increasing the overall mean (7.21%).

Diagnosis of MRONJ

The variation in incidence based on the method of diagnosis is interesting. In the group diagnosed by clinicians (42 studies), the mean incidence was higher (5.00%) compared with that from all 92 studies (4.30%). This could represent greater inclusion of cases in one group versus the other due to clinical knowledge. For example, patients self-reporting MRONJ in a study with stage 1 MRONJ, according to AAOMS, may be asymptomatic and therefore unaware they have MRONJ unless examined by a clinician. Therefore, these patients would be omitted in purely self-reported studies, causing an underestimation of incidence. Additionally, self-reporting patients may present an issue with the validity of diagnosis if not confirmed by a clinician. The variation in incidence numbers was seen across each population group analysed, 'Oncology', 'Osteoporosis' and 'Osteoporosis+Oncology', except the 'Other' group. Within the 'Other' population, the mean incidence for clinician-diagnosed was 2.19% versus 2.55% for all the included 92 studies.

Several studies reporting data from healthcare databases and insurance claim databases, in various countries, were also included in the review. These studies contain large numbers of participants, often in 10 000s, which is of benefit when analysing low-incidence events such as MRONJ. One limitation of these studies is the identification of MRONJ cases, frequently done using generic diagnostic codes rather than diagnosis by clinicians using the AAOMS classification. The use of International Classification of Diseases (ICD) codes, which are ordinarily used in hospitals for diagnostic coding, has several issues. In some areas, and in previous years, there was no specific code for MRONJ, and therefore other diagnostic codes were used as surrogate measures. These included those for inflammatory conditions of the jaws alongside an additional code for operative management. Again, this poses validity issues as other conditions such as osteoradionecrosis and osteomyelitis would fall under this coding umbrella leading to an inaccuracy in numbers. Additionally, MRONJ cases not requiring operative management may be omitted. This further illustrates the need for specific diagnostic reporting and coding to avoid these issues. This type of study does, however, illustrate the usefulness of collating data on a large scale, and when recorded accurately presents the opportunity for health surveillance of rare conditions as it presents a large number of participants in an easily accessible format.

Geographical location of the study

When reviewing mean incidence based on the continent in this 5-year period, studies conducted in Australia and Europe report far higher rates than all other groups (10.10% and 6.46%, respectively, vs 0.56% to 2.74% across all other locations). The included European studies were predominantly oncology studies (n=25), which could account for the overall higher incidence rate; two of the three from Australia were also oncology studies with fairly low numbers of participants (1316), again which may increase the incidence.

This analysis highlights potential differences in publishing patterns based on continent and research themes, which in turn may be influenced by variation in population numbers and incidence of diseases requiring drugs such as antiresorptive and antiangiogenic medications between continents. For example, breast cancer incidence rates in Eastern Asia in 2020 were 24.40% (551636 cases) compared with Australia/New Zealand with an incidence of 1.00% (23277).[16] Additionally, it is entirely possible that different continents have different treatment pathways, protocols, dosages, etc of medications for these conditions, which may also contribute to variation in incidence rates of MRONJ across regions. Additionally, some countries may have different reporting strategies of pathologies and different healthcare surveillance lending itself to large-scale data gathering and subsequent publication. Further variation in incidence between countries and continents may also be related to genetic variation. It is reported that several single nucleotide polymorphisms are associated with an increased risk/development of MRONJ, and it is entirely possible that these are found more commonly in certain populations and areas.[10 17]

Follow-up period

As reported above, multiple studies had a short follow-up period of only a few months. As the action of some medications, namely bisphosphonates, can persist for months or years after cessation of treatment, a longer follow-up period in studies may provide a more accurate representation of the incidence of this condition.[18] Furthermore, time on medications can also influence MRONJ development as described above. It is appreciated, however, that there are limitations within studies, and it may not be feasible (practically or financially) to follow-up patients for years, particularly in studies with large numbers of participants.[6] This is where other study types, such as healthcare database searches, can be useful for monitoring purposes.

Strengths and limitations

We acknowledge that within this review there is significant heterogeneity between studies across many

variables, and therefore there are clear limitations with the use of this extracted data. This project aimed to examine a large amount of data in an inclusive manner, providing an overview of the condition, evident from the total participant number of over 1 million. While definitive conclusions cannot be drawn based on the details of specific medications, duration of medications or pathology, this review provides some interesting exploratory findings that help expand knowledge and raise interesting discussion points based on international literature.

We have illustrated the impact that participant number, population type and diagnosis can have on reported incidence, highlighted issues with gathering MRONJ data and identified many areas of epidemiological MRONJ research worthy of dedicated further work. The findings of this review were shared with the SDCEP group during a review of its 'Oral Health Management of Patients at Risk of Medication-related Osteonecrosis of the Jaw' guidance. This highlights the importance of sharing information even prior to publication.

The information offered in this review provides useful insight to prescribers regarding risk and can support both clinician and patient decision-making. Further knowledge on incidence also highlights the level of clinical need within populations, which may facilitate appropriate allocation of services. This work therefore offers potential benefit to patients and medical and dental professionals in primary and secondary care.

Future work: proposed reporting of MRONJ in studies

To aid the harmonisation of information in studies, reporting MRONJ using an agreed criterion, likely the AAOMS classification, and including details regarding diagnosis, medications involved, duration of treatments and indication for those, would prove incredibly useful to collaborate data across studies involving this patient group. While drug reporting mechanisms exist, such as the yellow card reporting system in the UK, these are used sporadically; therefore there is a clear need for an agreed worldwide reporting strategy to improve aggregation of information with clear benefits to patients and providers. This was highlighted in a recently published review on MRONJ and echoed both by SDCEP and AAOMS in previous publications.[4 8 19]

The research team has developed a multisite database of MRONJ cases with multiple sites in the UK to be launched soon. This will provide a standardised method of data collection, according to agreed diagnostic criteria, which will eliminate some of the issues above. It will also present the opportunity to identify new drugs potentially causing MRONJ in this ever-changing field and monitor outcomes relating to management strategies. Furthermore, this information can feed into guideline generation, planning of services and ultimately improving the outcomes for these patients.

Conclusion

Heterogeneity in the aims and methods used in studies reporting MRONJ incidence impacts results and conclusions. This review is not absolute and has clear limitations. However, grouping together a large number of studies reporting MRONJ incidence and highlighting the difficulties with published data in this area is incredibly useful to gain insight and propose areas for future work.

Standardised, contemporaneous reporting of MRONJ cases would eliminate this variation and provide valuable insight into the epidemiology, natural history and outcomes of these patients, supporting evidence-based management and service provision of patients affected.

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