Up to 7% of referrals to oral and maxillofacial surgery are related to medication-related osteonecrosis of the jaws: how much is really out there?

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INTRODUCTION: Medication-related osteonecrosis of the jaws (MRONJ) is generally described as rare; therefore, firm incidence data are challenging to ascertain.

AIM: Using two sites in Northwest England, ascertain the number of referrals to oral and maxillofacial surgery involving:

- Suspected MRONJ.
- Patients at risk of MRONJ requiring a dentoalveolar procedure.

METHOD: All sequential referrals over a 2-year period were analysed. The referrals were categorised into ‘type’ of referral (stage 1). Any referral for MRONJ, or patient at risk, was then further examined (stage 2).

RESULTS: A total of 2150 referrals were screened. The most common referral reasons were temporomandibular joint issues and hard tissue conditions. The proportion of referrals for suspected MRONJ was similar for both sites: 3.7% (site 1) and 3.4% (site 2). At site 1, 1.6% of all referrals were at risk of MRONJ referred for treatment. In site 2, 3.8% of all referrals were in this category.

CONCLUSION: Despite limitations, the finding that patients with or at risk of MRONJ potentially equates to 7% of all referrals represents a substantial proportion of OMFS practice. Therefore, there are clear benefits of collecting accurate data prospectively to understand the scale of this condition and its impact on services.

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INTRODUCTION

Medication-related osteonecrosis of the jaws (MRONJ) was first described in 2003 by Marx et al. Since 2003, awareness of MRONJ has grown exponentially with countless publications on the subject. The nomenclature has also evolved from bisphosphonate-related ONJ to antiresorptive-related ONJ to MRONJ, reflecting the implication of drugs other than bisphosphonates in the development of MRONJ, namely antiresorptive and some antiangiogenic medications.

MRONJ is generally described as rare; however, it is not an uncommon presentation to oral surgery and oral and maxillofacial surgery units. Despite this, firm incidence (and hence prevalence) data are hard to ascertain. The risk of MRONJ is largely estimated at less than 1% of those at risk and influenced by numerous factors such as indication for the implicated drug, modality of drug, extent of any dentoalveolar surgery carried out and co-morbidities, etc.

Attempts to ascertain national UK MRONJ incidence data have proved challenging due to difficulties collecting source data from surgical units. In addition, cases may be misdiagnosed as other pathologies such as osteomyelitis and therefore omitted from data collection. Fedele et al. also discussed that patients with the non-exposed bone variant of MRONJ may be missed in MRONJ case data collection, again leading to incorrect incidence data. There are some large clinical trials of specific drugs reporting incidence of MRONJ; however, strict exclusion of patients requiring dental treatment mean results may not be generalisable.

As numbers are low, cases are often seen sporadically by a range of clinicians across a large number of units. Without the mechanism to collate these data, the true number of MRONJ cases is currently unknown. Furthermore, due to the lack of agreed consensus on managing MRONJ patients, case management is variable, as is disease resolution. Treatments can range from simple symptom management up to large resection and subsequent reconstruction. These factors may potentially have a huge impact on service planning, provision of care and resource management. Therefore, there is a clear need to establish the firm incidence and outcome data relating to different management strategies in this country, a comment echoed by Cochrane, SDCEP and AAOMS.
Patients at risk of MRONJ requiring a dentoalveolar procedure.

Referral data at the source of initial receipt were examined to explore the extent of potential MRONJ cases and those at risk of MRONJ. Two sites were used for analysis: site 1 is a teaching hospital (TH) and site 2 is a district general hospital (DGH). All sequential referrals to both sites from 1 November 2016 for a period of 2 years were collected. An automated search was considered to screen large numbers of referrals but dismissed as many referrals were handwritten. Therefore, referrals were hand searched and screened in totality to avoid omissions. Referrals were analysed in two stages described below. Referrals were fully anonymised prior to assessment in compliance with the ICO guidelines on secondary use data and the study was undertaken under a service evaluation model hence ethical approval was not required.

Stage 1—Referral overview and screening

Referrals were categorised into ‘type’ of referral under broad headings including hard tissue (such as dentoalveolar procedures), soft tissue, oral medicine (oro-mucosal conditions, facial pain), salivary gland, temporomandibular joint complaints and miscellaneous (for any others). This provided an overview of the service in each unit based on the distribution of types of referrals received. Each referral was reviewed in entirety regardless of referral type to avoid omission of possible cases.

Any potential referral for MRONJ or patient at risk of MRONJ requiring surgical intervention was selected for further analysis in stage 2.

After removal of duplicates, 1465 referrals to the TH and 649 referrals to the DGH remained. Stage 1 analysis can be seen in Table 1.

Within the TH site, the most common referral reason was temporomandibular joint issues, 45% of all referrals (66 patients). In the DGH site, the most common reason for referral was hard tissue conditions, 46% of all referrals (298 patients).

Stage 2—Referral refinement for possible MRONJ cases/patients at risk of MRONJ

All possible cases of MRONJ or patients at risk of developing MRONJ were further analysed as two separate categories and the following data were extracted: referral type, clinical description, age and sex. A diagrammatic illustration of the search can be seen in Fig. 1.

Referrals of possible MRONJ cases

There were 54 referrals for possible/established MRONJ to the TH accounting for 3.7% of all referrals. There were 22 referrals for possible MRONJ to the DGH, accounting for 3.4% of all referrals. The features noted in the referrals are illustrated in Table 2. In TH referrals for possible MRONJ, the most common feature described was osteonecrosis/MRONJ (37%, 20 cases) or poorly healing socket (30%, 16 cases). The most common reported feature in DGH referrals was exposed bone (23%, 5 cases) or pain after extraction (18%, 4 cases). Interestingly, those referred for suspected MRONJ made up 3% of all referrals to both sites, representing a significant proportion of new patients.

Most patients referred for possible MRONJ to the DGH were female, 73% (16 patients), mean age was 65.7 years (range 31–85 years). Those referred to the TH had a similar gender distribution: female (66%, 36 patients) vs male (32%, 18 patients). The average age was slightly lower at 61.3 years (range 32–88 years).

Referrals for dentoalveolar surgery in patients at risk of MRONJ

A total of 1.6% (23 patients) of all TH referrals were patients at risk of MRONJ referred for treatment (i.e., extractions or dentoalveolar surgery). The majority were female, 82% (19 patients), mean age was 68 years (range 50–92 years). A total of 3.8% (25 patients) of all DGH referrals were in this category comprising of 11 patients noted as ‘at risk’ in the referral, and an additional 14 patients possibly at risk (from features in referral). In all, 72% (18 patients) were female and 28% were male (7 patients), mean age was 75 years (age range 51–89 years). It was noted that those referred to OMFS DGH had an older profile in both the ‘at risk’ and the ‘suspected’ MRONJ groups than those referred to the TH.

When analysing the DGH referrals, there were several patients identified as ‘possibly at risk’ by the reviewer based on features.
documented in the referral. These patients were not explicitly stated as at ‘risk of MRONJ’ in the referral; however, the information provided from the referrer indicated a possible risk of MRONJ. This included, for example, a patient with osteoporosis but with no medication history included in the referral. Therefore, these referrals were classified as ‘possibly at risk’ in the results section. For the TH patients, none of the referrals were identified in this grouping. The only ‘at risk’ referrals included for the TH implicitly stated that the patient was at risk of MRONJ.

**DISCUSSION**

**Overview**
The most common ‘type’ of OMFS referral to both units was hard tissue conditions and temporomandibular joint issues. The distribution however varied between the sites, likely due to the organisational setup of these services. Within the surrounding area of the DGH there may be fewer tier 2 services offering dentoalveolar surgery, hence, the large number of referrals for this type of treatment to OMFS. Tier 2 oral surgery services are a commissioned service in England that carry out oral surgery procedures on referral from primary care. These cases are deemed too complex for general dental practice and therefore require a practitioner with additional skills. The referral practices that commonly refer to the TH have access to a large number of dentoalveolar surgical services (tier 2) and therefore less referrals of this type are referred into the hospital. In addition, this unit offers a dedicated TMD clinic, an example of possible provider-induced demand seen in the referral profile.
MRONJ

Interestingly, the proportion of referrals for suspected MRONJ was similar for both sites; 3.7% of all referrals to TH and 3.4% to DGH. Considering the volume of new OMFS referrals each month, this equates to a substantial proportion of the workload. In addition, potentially 1–2% of all referrals to OMFS were for the treatment of patients at risk of developing MRONJ. This figure is similar to salivary gland pathology referrals, 2.7% DGH vs 1.6% TH, which is considered very much part of normal OMFS practice.

One study based at a DGH OMFS site reported that from a sample of 58 patients at risk of MRONJ who had dentoalveolar surgery, 20 subsequently developed MRONJ (approximately 35%) [13]. These patients were a mixture of high and low risk patients taking antiresorptive medications for various cancers and osteoporosis in IV and oral form, the majority in the latter group (13 patients) [13]. With 3 million people in the UK with osteoporosis and nearly 5000 new cases of multiple myeloma diagnosed each year, just two groups potentially at risk of MRONJ – osteoporosis and nearly 5000 new cases of multiple myeloma (13 patients) [13]. With 3 million people in the UK with osteoporosis in IV and oral form, the majority in the latter group taking antiresorptive medications for various cancers and osteoporosis in IV and oral form, the majority in the latter group (13 patients) [13]. With 3 million people in the UK with osteoporosis and nearly 5000 new cases of multiple myeloma diagnosed each year, just two groups potentially at risk of MRONJ – osteoporosis and nearly 5000 new cases of multiple myeloma (13 patients) [13]. With 3 million people in the UK with osteoporosis and nearly 5000 new cases of multiple myeloma diagnosed each year, just two groups potentially at risk of MRONJ – osteoporosis and nearly 5000 new cases of multiple myeloma (13 patients) [13].

As a result, a prospective multisite registry is currently in development to be rolled out for use across the UK. MRONJ lends itself well to a database due to the established classification and staging criteria [2]. In addition, due to the nature of the condition, patients are highly likely to be sent to a limited number of specialties; mainly oral surgery and oral and maxillofacial surgery. This consolidates the patient journey and hopefully lends itself to the collection of this data.

CONCLUSION

By collating much larger data sets on MRONJ cases than has previously been possible in the UK, patterns may emerge, informing decision making regarding these patients and ultimately improve patient care. Only then, when we have begun to combine this data on a wide scale will we be able to assess the true extent of MRONJ and design services accordingly to tackle this difficult to treat condition.

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AUTHOR CONTRIBUTIONS
AC: data collection, analysis of data and writing of the manuscript. IP: design of project, analysis of data and editing of the manuscript.

COMPETING INTERESTS
The authors declare no competing interests.

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