

Management of Medication-related Osteonecrosis of the Jaw (MRONJ) risk in patients due to commence anti-resorptive/anti-angiogenic drugs – how should pre-drug-treatment dental preventive care be organised?

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Background: Medication-related osteonecrosis of the jaw (MRONJ) can be difficult to treat and causes significant morbidity, but is largely preventable. Published guidelines strongly recommend dental assessment and necessary remedial treatment before such drugs are commenced. Specific guidance on who should provide or arrange this care is lacking, and it may often be delegated to the patient arranging it with their own dentist. However, numerous factors can make this difficult. **Aims:** To review published strategies for organising timely and effective dental preventive care in patients due to be prescribed MRONJ-associated drugs. **Results:** 13 studies were identified giving some detail of formal dental assessment setup. Two comprised a primary care dentist-led service, one a hospital assessment with most treatment in primary care and the remainder a hospital-based service from dental staff with or without dental specialists and input from medical and allied professionals. Follow-up varied from none to the period of drug use. Most studies reported the effectiveness of the service in reducing MRONJ incidence. **Discussion:** Details of the organisation of dental assessment/treatment are incomplete in most studies. Direct comparison is difficult. However, promising strategies to prevent MRONJ have been demonstrated. **Conclusion:** There exists a large and growing group at risk of MRONJ who have significant amounts of oral disease. However, the risk of the condition is largely preventable. Promise is shown in several methods to organise timely dental care before treatment.

Keywords: Oral health, older adults, prevention, osteonecrosis

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) was originally defined as exposed bone in the maxillofacial region persisting over 8 weeks in a patient taking a bisphosphonate with no previous jaw radiotherapy (AAOMFS, 2007). However, a variant with no exposed bone is now well-recognised (Fedele *et al.*, 2010). MRONJ can cause considerable morbidity and be difficult to treat. It is incompletely understood but hypothesised to result from inhibition of bone remodelling and angiogenesis, inflammation and/or infection and microtrauma (Ruggiero *et al.*, 2014).

Originally only bisphosphonates were known to cause MRONJ, but a range of antiresorptive and anti-angiogenic drugs used to treat osteoporosis and solid tumour and haematological malignancies are now implicated. Use of these drugs is increasing. Bisphosphonate prescriptions increased 10-fold from 1996–2008 (NHS Digital, 2006; ONS, 2015) and continued to increase at a lower rate to 2014. In England in 2014 7,391,000 prescriptions for alendronic acid, 737,000 for risedronate sodium and 20,000 for denosumab were dispensed (ONS, 2015).

MRONJ in patients taking anti-resorptives for osteoporosis is rare at between 0.1% and 0.01% incidence (Rogers *et al.*, 2015), approaching that observed in placebo groups (Beth-Tasdogan *et al.*, 2017). The risk with annual intravenous (IV) or weekly oral preparations is similar (Grbic *et al.*, 2010).

An incidence of 0.052% was reported for patients with osteoporosis taking Denosumab (Bone *et al.*, 2017). IV bisphosphonates for a cancer indication carry a higher risk of 0.7 – 6.7% (Ruggiero *et al.*, 2014), Denosumab 0.7–1.9% (Ruggiero *et al.*, 2014, Chen *et al.*, 2016) and Bevacizumab 0.2% (SDCEP 2017). MRONJ is linked with Sunitinib, Everolimus, Afibercept and Temsirolimus in case reports only.

Dento-alveolar surgery is the major precipitant and the majority of cases follow dental extraction (Ruggiero, 2014). Other local risk factors are oral infection (periapical or periodontal), poorly-fitting dentures, poor oral hygiene and intra-oral trauma.

For this reason, guidelines have been published recommending dental assessment and remedial dental treatment before (or as soon as possible after for low risk patients) initiating MRONJ-associated drugs (Ruggiero *et al.*, 2014; SDCEP, 2017; Joint Formulary Committee, 2018; Hellstein *et al.*, 2011). All emphasise preventive care, removal of sources of dental infection (thus minimising the need for future extractions) and patient education about MRONJ, oral hygiene, diet, regular dental care, smoking cessation and symptoms warranting dental review. Two reviews have found low quality evidence for 3-monthly dental examinations and preventive treatment being effective in reducing the incidence of MRONJ (Beth-Tasdogan *et al.*, 2017, Poxleitner *et al.*, 2017).

When assessed, the dental treatment needs of patients with cancer before starting MRONJ-associated drugs are high. Of 211 patients in Italy, pre-bisphosphonates, 22.4% needed restorative treatment and 70.1% at least one extraction (Vandone *et al.*, 2012). In the United States, among 152 patients with cancer, only 33 required no treatment. One third (35%) of the dentate individuals required restorative, 32% periodontal treatment and 65% extractions (averaging 6 extractions each) (Chang *et al.*, 2017). Similar results were seen in the UK where 72% of dentate patients with cancer required extractions (average 3.73 teeth) (Patel *et al.*, 2015). Of 99 pre-antiresorptive patients in Wales, only 37 required no treatment (Muthukrishnan *et al.*, 2017). No studies can be found of the pre-treatment oral health needs of patients with osteoporosis.

Therefore there exists a large and growing group at risk of MRONJ (a problem to a large extent preventable) who have appreciable amounts of oral disease. Guidelines are therefore needed that indicate who should arrange and who should undertake the dental assessment and treatment, that are mindful of problems of access to care, patient factors, the dental profession and the need for effective communication.

Not all prescribers may highlight the need for a dental assessment. A survey of 29 UK General Practitioners (GPs) and Physicians showed only 20% referred for dental assessment before commencing bisphosphonates (Tanna *et al.*, 2017a). Referral levels of 30-66% have been noted elsewhere (Muthukrishnan *et al.*, 2017; Kim, 2016; Sturrock *et al.*, 2017; Akintoye *et al.*, 2016; Taguchi *et al.*, 2016). An audit of Scottish patients with metastatic breast cancer taking IV bisphosphonates showed only 2% of records contained documentation of dental health or advice regarding dental assessment (NHS, 2018).

Problems with access to dentistry are often overlooked, yet only 50.9% of the UK adult population visited an NHS dentist in the 24 months to March 2018 (NHS, 2016). The proportion attending regularly in 2009 was higher at 60% for all adults and 75% for ages 65-74, but falling thereafter with increasing age. This drop in regular attendance with older age corresponds with a period of increasing osteoporosis and cancer incidence (Hernlund *et al.*, 2013; ONS, 2016), and increasing oral disease (ADHS 2009). In the UK, there have been issues with access to NHS dental care for some years (ADHS, 2009; Steele *et al.*, 2009). The most recent UK data show 92% of adults who tried to book a dental appointment were successful (ADHS, 2009), 10% of which were with a dental practice they had not visited before. However, the delays to assessment or treatment completion were not measured. Patients with cancer should complete remedial treatment and allow 4-6 weeks post-extraction healing before starting drug treatment (Ruggiero *et al.*, 2014). Therefore, despite some reassurance from the available data, not all this group may obtain timely care in UK primary care dentistry.

Patients may feel reluctant to access dentistry for reasons of cost, lack of oral health awareness or dental anxiety (ADHS 2009). Between 18 and 32% of at-risk patients were aware of or could recall being informed of a risk of MRONJ (Bauer *et al.*, 2012, Migliorati *et al.*, 2010). A survey of patients with myeloma found a perceived delay to cancer treatment acted as a barrier to seeking dental assessment (Barker *et al.*, 2007).

Dental professionals' knowledge may also be a barrier to care. A survey of 129 UK-based General Dental Practitioners (GDPs) showed over 90% did not know that medications other than bisphosphonates were linked with MRONJ (Tanna *et al.*, 2017b). Although the treatment of patients before and (usually) during drug treatment is within the normal remit of GDP work (SDCEP, 2017), adequate knowledge and confidence to do so is not universal (Tanna *et al.*, 2017b). There may also be associated clinical governance and medico-legal concerns (Muthukrishnan *et al.*, 2017).

Finally, absent or poor communication between medical and dental teams has been noted (Muthukrishnan *et al.*, 2017; Sturrock *et al.*, 2017; Akintoye *et al.*, 2016). One study in Japan showed no cooperation between physicians and dentists in 72% of cases (Taguchi *et al.*, 2016).

In view of these potential barriers to accessing the care indicated in the guidelines, the rationale for this study was to identify means of better organising care for people at risk of MRONJ such that the barriers are minimised or eliminated. Such a study, utilising all published literature on the subject, has not previously been conducted. Therefore, this paper aims to review published strategies to organise preventive dental care for patients due to start MRONJ-associated drugs.

Materials and Methods

An online search was made using the Pubmed and Google Scholar databases. Keywords used (singly and in combination) comprised – BRONJ, MRONJ, bisphosphonate*, anti-resorptive, anti-angiogenic, osteonecrosis, prevent*, dent*, incidence, clinic, strat*. Any report describing a service aiming to prevent MRONJ in susceptible patients, regardless of the overall purpose of the study, was included. There were no date or language restrictions. Reports from any form of healthcare environment worldwide were included. There were no exclusion criteria. Abstracts were read and full texts retrieved for relevant studies, the references of which were checked for further studies.

The approach used for analysing the included studies in order to categorise the results was qualitative content analysis (Green and Thorogood, 2010). For the purposes of this paper, a relatively simple form of thematic analysis was sufficient. Initially the full texts were read and re-read in order to immerse in the paper content. From there, recurring or common themes could be identified and listed, before being coded into groups that described related entities. These codes comprised lists of different clinic settings, staff members, services, e.g. extractions, restorative, periodontal etc., recall periods and referrals. These codes were then grouped into linked categories – setting and staffing, services provided, referrals/entry into service and recalls/follow-up. These are thus the categories of data analysis presentation in the results. Overall, these were largely a reflection of their frequency of occurrence in the text, with the assumption that this represents a proxy for significance (Vaismoradi *et al.*, 2013). This is believed to be a more objective and systematic means of identifying themes in content analysis, and more reflective of the surface meaning of the text (Bloor and Wood, 2006).

Table 1. Summarised details of included studies

Study Country	Study Design	Setting	Patient population	Route into service	No. patients	Intervention Group dental assessment/treatment	Comparison Group	Follow-up	MRONJ Outcomes	Further Analyses
Dimopoulos (2009) Greece	Cohort with control	GDP for assessment and treatment OMFS in hospital for extractions	Multiple myeloma patients receiving IV zolendronic acid	All patients in the institution undergoing this treatment included, no further details	90 in intervention group 38 in comparison group	Assessment and treatment by "their dentist". Extractions in hospital No further details given	Retrospective analysis of before programme introduced	Not described	Incidence rates per 100 person months 0.671 and 0.230 in comparison and intervention groups respectively	None
Muthukrishnan (2017) UK	360 degree service survey	Multi-disciplinary, cross-service preventive pathway using primary dental care, CDS and hospital services	Patients planned for IV BP or denosumab therapy for cancer	Referral from oncologists and haematologists	99 referrals received	Pathway established to enable rapid access to patient's own dentists for preventive care/treatment before drug initiation. Care networked with the community dental service for those not registered with a dentist. Urgent referral to secondary care for opinion/treatment.	None	Not discussed	Not part of study	75% of patients assessed by GDP 16% assessed by CDS 8% seen in secondary care. 90% of patients, 75% of GDPs, all oncologists and CDS dentists satisfied.
Chang (2017) USA	Cost analysis study	Hospital BP clearance clinic" (inpatients and outpatients)	Veterans due to be prescribed any form of anti-resorptive medication for any indication	Referred by "physician", no further details given	152	Comprehensive clinical and radiographic examination. Standard prophylactic measures, restorative/endodontic treatments and extractions as necessary by one dentist and one dental assistant No further details given	None	Precluded 6-monthly recalls, no further data given	Not measured	Cost to run service = \$131,700 per patient for treatment and 7y follow-up
Ripamonti (2009) Italy	Cohort with control	Dental team in hospital and Oncology Unit outpatient clinic	Patients with cancer due at least one clinic infusion of pamidronate, zolendronate or clodronate	Referral from oncologist	154 in intervention group 812 in comparison group	Clinical inspection by hospital dental team (no further description). Preventive care and remedial "oral sanitation", i.e. restorative and extractions, provided. No further details given	Retrospective analysis of patients before programme introduced	6-monthly treatment	Incidence rate per year 0.029 and 0.014 in comparison and intervention groups respectively	None

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Sim (2015) Australia	Cohort with control	Dental oncology department in specialised cancer hospital	All cancer patients at the unit due to commence anti-resorptives	Dental department responsible for care of 637 in all patients, no group further details given	Dental assessment including oral examination. No further details given	Retrospective analysis of 6-monthly patients before preventive programme introduced	76% reduction in incidence in intervention group	None
Bonacina (2011) Italy	Cohort with control	Hospital Department of Dentistry	Patients pre-treatment with IV zolendronate, all for cancer indication	Referred from Department of Oncology – no to BPs further details given	Provided by the “department of dentistry” Thorough clinical examination Professional oral hygiene and any necessary periodontal/restorative/surgical treatment provided No further details of service set-up	Patients who had received BPs. Visited the dental clinic and had radiographic assessment. Informed of risks of MRONJ. Oral hygiene and dental rehabilitative treatment offered if necessary	Intervention group no cases detected in 18 months follow-up. Comparison group 3/65 had MRONJ at initial visit & 7 more cases over 18 month follow-up	None
Bramati (2015) Italy	Cohort without control group	Department of Dentistry at University of Milan	Patients attending department of oncology for IV zolendronic acid/pamidronic acid	All consecutive patients attending oncology department recruited	“Odontoiatric team” [sic] – 2 dentists, 1 oral surgeon, 2 nurses, 3 dental hygienists. All patients initially saw a research nurse to collect medical history and details of risk factors. Initial assessment and professional oral hygiene. Any remedial treatment provided. All patients also had appointment with dental hygienist	None	Patients with good oral condition reviewed 6-monthly. Those with poor oral condition reviewed weekly until good, then 3-monthly. All also examined by oncologist	None

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Taylor (2015) UK	Case series	Hospital Specialist BP Clinic	Any patient on service referred into and undergoing extractions (un-clear if the clinic only sees those needing extractions or for this study only)	Patients referred from dental hospital, oncology, rheumatology, orthopaedics, GPs and GDMs	225 (202 on oral and 23 on IV BPs)	Initial assessment by multidisciplinary team – 2 oral surgery consultants, 2 restorative dentistry consultants. Only those requiring extractions included in this study. Clinical examination undertaken – it is implied any remedial treatment provided.	After extractions at 2 weeks, 2 months, 6 months and 1 year (more frequently if on IV therapy)	13/225 patients diagnosed with MRONJ (5/202 on oral and 8/23 on IV therapy)	None
Patel (2015) UK	Case series	Hospital dental clinic, dedicated for pre-IV BP cancer patients	Any patient due to start IV BP referred into the service.	90.3% referred by oncology (doctors & oncology nurses) and 9.3% by GDMs	62	Led by consultants in special case dentistry and oral surgery. Assessment and necessary extractions. For restorative, periodontal or prosthodontic work, patient advised to see GDP and "a letter sent". Patients unsuitable for primary care seen in special care department	No follow-up	Not measured	None
La Verde (2008) Italy	Retrospective control	Retrospective-Oncology department hospital	Patients treated with IV BPs for bony metastases	All patients treated in the institution between the study dates	Preventive group – 117 patients, of which 50 commenced before preventive programme but later received the prevention. Control group - 69 patients whose drugs started before preventive programme instituted, and did not receive prevention	Oral cavity clinical examination by oncologist Dental evaluation by dentist "in specialised centre" for all patients with oral cavity-related symptoms Patient education No further details given	Radiology exam. No further details	8 patients from each group diagnosed with MRONJ	None

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Mucke (2016) Germany	Hospital Department of Oral and Maxillofacial Surgery	Patients with bony metastases from prostate adenocarcinoma, due to receive IV zolendronic acid	Urology and Oral & Maxillofacial Depts. No further details of recruitment or randomisation	Group A - Initial examination at the Department of Oral and Maxillofacial Surgery (OMFS), if necessary planned to be treated by the patient's dentist once a year. No preventive treatment strategy in place Group B - examined and treated by the OMFS team. Included extractions, restorative, periodontal and endodontic (by specialist) as needed	Group A evaluated at least once a year by OMFS team Group B at least 4 times 3-monthly	MRONJ recorded in 38/163 patients in Group A and 2/90 in Group B. Incidence proportions 23.3% and 2.2% respectively	None
Catania (2016) Italy	Multi-disciplinary oncology-haematology department	Multiple myeloma patients planned for treatment with IV pamidronate or zolendronate	All patients eligible to start BP treatment	Prevention group - patients after both MDT and prevention strategy implemented Historic group - started drugs before MDT recognised as an entity. Screening group - started drugs after MDT instituted but before prevention programme. All patients assessed by dentist when programme set up or assessment process	Patients followed up, but occurred in 14.2% of historic, 10% details given of screening and 0% of prevention groups	None	None
Vandone (2012) Italy	"Interdisciplinary care group" in hospital	Cancer patients with bone metastases treated with IV BPs	Not described	Preventive group assessed in presence of oral surgeon and medical oncologist. Retrospective before programme instituted	Professional oral hygiene every 3-4 months Oral examination every 6 months X-ray and CT exam annually	2.8% in prevention group developed MRONJ over 47 months	None

BP = Bisphosphonates

CDS = Community Dental Service

RCT = Randomised controlled trial

Results

Thirteen reports were identified that described some type of formal dental assessment for patients due to be prescribed relevant drugs, originating from the UK, USA, Australia, Germany, Greece and Italy, all published since 2008.

Study Design and Population

Eleven reports only included patients with cancer (9 of which only included those due to receive IV bisphosphonates and 2 accepting any anti-resorptive), one included patients taking bisphosphonates for any reason (Taylor *et al.*, 2013) and one included any anti-resorptive for any indication (Chang *et al.*, 2017). Seven reports described a preventive dental service and compared its outcomes with those before the programme was instituted. One study reported a randomised controlled trial comparing two groups enrolled in different preventive regimens (Mucke *et al.*, 2016). Five reports described a service and made no comparisons. Ten of the 13 studies reported MRONJ outcomes, one performed a financial analysis and one assessed patient/staff acceptance of the service.

Setting and Staffing

Two reports described GDPs in primary care as the principle providers of assessment and preventive care/treatment. In one preventive programme (Dimopoulos *et al.*, 2009), patients with myeloma from a hospital in Greece were assessed by “their dentist” before initiation of IV zoledronic acid. The dentist provided any necessary remedial work. Any “major procedures like extraction” were carried out by an oral and maxillofacial surgeon (OMFS) in hospital. A detailed report from 3 Welsh health trust areas (the referral hinterland of one OMFS and special care dentistry department) described a MRONJ risk reduction pathway (Muthukrishnan *et al.*, 2017). This multi-disciplinary, cross-service, cross-health-board pathway aimed to facilitate referral of pre-drug-treatment cancer patients to their own GDP, to be seen within 6 weeks. Stakeholders were consulted and the plan drawn up over a 2 year period. A part-time oncology coordinator served as a central point of patient contact. The Community Dental Service (CDS) provided initial stabilisation care for patients not registered with a dentist, before transfer to a shared care plan with a GDP for ongoing care. The local special care dentistry managed clinical network, a multi-organisation linked network of professionals aiming to overcome restrictive organisational boundaries, was seen as crucial. A protocol for urgent referral from GDPs to secondary care was also incorporated, supported by postgraduate training. After one year, 76% of patients had seen GDPs, 16% the CDS and 8% secondary care clinicians. It was noted resources were insufficient to set up a specialist hospital clinic. This is the only study to involve the CDS.

The remaining 11 reports describe hospital-based dental services, many in dedicated departments. However, four of these make no mention of the staffing of the service beyond it being a hospital dental department. Four specifically mention the presence of dentists (this is implied in the remaining studies). There was one cost-analysis study of a service that used a dentist and dental assistant (Chang *et al.*, 2017).

In one report, patients received an oral examination and education from an oncologist and were referred for a dental evaluation in a “specialised centre” if any oral-cavity-related symptoms were present (the proportion requiring this further step is not given) (La Verde *et al.*, 2008). Importantly therefore, the examination was conducted by a medically, rather than dentally-trained staff member unless specific oral symptoms were present. This was the only included service incorporating this design, but no further details were given.

Four services included dental specialists as part of a team, variously including oral surgeons, restorative dentists, special care dentists and endodontists. Two others included OMF surgeons. An “odontoiatric team” [sic] at a hospital in Italy comprised two dentists, one oral surgeon, two dental nurses and three dental hygienists (Bramati *et al.*, 2015). Interestingly, every patient initially saw a research nurse (the only study describing use of this group) who collected details of the medical history and risk factors, and all patients saw a dental hygienist, although no further details are given. This is also the only report to mention hygienists specifically, although several others may have involved them but do not give complete descriptions. In one “interdisciplinary group” each patient underwent a thorough clinical examination in the presence of an oral surgeon and medical oncologist (Vandone *et al.*, 2012). The exact make-up of the service, besides these personnel, is not mentioned. However, dental examination and many treatments would not fall within the usual remit of either of these specialties, and therefore the details may be incomplete. A “specialist bisphosphonate clinic” comprised two oral surgeons and two restorative dentistry specialists (Taylor *et al.*, 2015). Another clinic serving patients with cancer pre-IV-bisphosphonates comprised oral surgery and special care dentistry consultants (Patel *et al.*, 2015), although this service only provided certain treatments and directed patients to their GDP for the remainder. Patients without a GDP were treated in the special care dentistry department, although no specific details are given. This is the only report identified where patients were assessed in hospital and directed to seek treatment in primary care (except for the control group in the randomised controlled trial (Mucke *et al.*, 2016)). Here, patients were assessed by OMF Surgeons and “planned to be treated by the patient’s dentist once a year”, with little further information. The intervention arm in the trial was not described in complete detail but comprised a service led by OMF Surgeons who performed an assessment and provided some treatment, involving an endodontist if needed (Mucke *et al.*, 2016).

One large multi-disciplinary team involved dentists, OMF surgeons, haematologists, oncologists, nurses, radiologists, nuclear medicine and infectious diseases specialists (Catania *et al.*, 2016). Patients were discussed at meetings but limited further details are given beyond assessment and treatment being provided by the dentist.

Services Provided

Two studies gave little information, with detailed description limited to the provision of dental assessment (Sim *et al.*, 2015) and dental evaluation (La Verde *et al.*, 2008), whilst implying a comprehensive preventive service was offered.

The two primary care studies included one where all treatment except extractions (which were referred into hospital OMFS) was done in that setting (Dimopoulos *et al.*, 2009). The other described a framework where assessment and treatment was undertaken by GDPs with specially developed referral pathways from hospital practitioners, with links into the CDS and hospital OMFS services if needed or for patients not registered with a dentist (Muthukrishnan *et al.*, 2017).

The service described by Patel *et al.* (2015) provided examination, preventive advice and extractions by special care dentists and oral surgeons. Assessment was carried out in their hospital clinic, and if restorative, periodontal or prosthodontic treatment was needed, patients were “advised to see their GDP...as soon as possible and a letter sent”. Taylor and colleagues (2013) analysed only extractions seen in a hospital bisphosphonate clinic, but implied that all necessary restorative work was ordinarily carried out by the department.

In the remaining seven reports hospital services provided assessment and all necessary preventive work/remedial treatment. Three provided any and all necessary care in a service comprising either just dentists or with limited practitioner information (Chang *et al.*, 2017); Ripamonti *et al.*, 2009; Bonacina *et al.*, 2011).

One service provided all care via its team of dentists, dental nurses, oral surgeons and hygienists (Bramati *et al.*, 2015), one by a dentist working within a large multi-disciplinary team (MDT) (Catania *et al.*, 2016) and one after assessment by an oral surgeon and oncologist (Vandone *et al.*, 2012). These reports variously mention providing restorative, periodontal and surgical care and professional cleaning/hygiene.

The treatment arm in the trial provided all care led by OMF surgeons, with involvement of endodontists where needed (Mucke *et al.*, 2016). No further details of the staffing of this service is given, leaving some uncertainty as dental examination and treatments such as restorative and periodontal work fall outside the normal remit of an OMF Surgeon and endodontist. Similar uncertainty exists in the study by Vandone *et al.* (2012) where each patient was examined in the presence of an oral surgeon and medical oncologist. The exact make-up of the service, besides these personnel is not described. An “informative letter” to the patient’s GDP was also provided, including information about MRONJ risk, management and the group’s contact details. This is one of very few mentions of communication between hospital and primary care services in the reports.

Referrals/Entry into service

Only one study (Vandone *et al.*, 2012) did not give any details of referrals into the service. The service where GDPs assessed and treated patients with myeloma due to receive IV bisphosphonates saw all patients within ‘their institution’, but gave no further details of referral mechanisms (Dimopoulos *et al.*, 2009). The preventive pathway reported by Muthukrishnan *et al.* (2017) accepted referrals from oncologists and haematologists, then seen largely by primary care GDPs. Chang *et al.* (2017) accepted patients taking any anti-resorptive for any reason as referred by their physician, but gave no further details of the referral mechanism.

The randomised controlled trial recruited patients with prostatic adenocarcinoma via the urology and OMFS departments, and again give no further details (Mucke *et al.*,

2016). This comprises the most limited population among the reports, as no others discriminated between cancer types but included patients with any form of malignancy.

Of the 9 further reports working with patients in oncology institutions, six stated they would see all patients due to be prescribed IV bisphosphonates and several described referrals from oncologists. One accepted referrals from GPs, GDPs, the dental hospital, orthopaedic surgeons and rheumatologists to their specialist bisphosphonate clinic (Taylor *et al.*, 2013). Another reported 90.3% of patients referred to its dedicated clinic for pre-IV-bisphosphonate cancer patients were referred by oncology (Patel *et al.*, 2015). Interestingly, of 93 referrals to the service in the study period, seven patients did not attend.

Recalls/Follow-up

Recalls and follow-up were not described in four reports (including Dimopoulos *et al.*, 2009 and Muthukrishnan *et al.*, 2017) and one mentioned radiographic review only, with no further details. The report by Patel *et al.* (2015), in which patients were assessed in hospital then treated by GDPs (or special care dentists in hospital if unsuitable) states it provided no follow-up. Five of the services based in dental departments treating oncology patients provided 6-monthly follow-up (one stating more regular if poor oral condition), one of which also included 3-monthly oral hygiene appointments. Patients in the randomised controlled trial intervention arm (Mucke *et al.*, 2016) were examined “at least 4 times” 3-monthly, compared to once a year in the control group.

After extractions, patients seen in the specialist bisphosphonate clinic (Taylor *et al.*, 2013) were followed-up at 2 weeks, 2 months, 6 months and 1 year, with recalls “more frequently” if on IV therapy.

Discussion

This study aimed to review published strategies to organise preventive dental care for patients due to start MRONJ-associated drugs to be used as an evidence base to inform clinicians and healthcare managers seeking to design or set up services. Thirteen reports were identified involving a service existing for the purpose of preventing MRONJ.

Most reports describe hospital-based dental services. Some included medical and allied professionals in an MDT clinic, or a system of referral. Dental assessment was variously by dentists, or Consultants in restorative dentistry, special care dentistry, oral surgery or OMFS, either singly or in combination. Treatment was provided either wholly or partly (extractions only (Patel *et al.*, 2015)) by this hospital service, or by GDPs (Muthukrishnan *et al.*, 2017, Dimopoulos *et al.*, 2009). The requirement for dental specialists to assess and treat, rather than GDPs, is questionable. Guidelines stress most patients can be managed by GDPs (SDCEP, 2017). GDP-based systems have been shown to be acceptable to patients and clinicians (Muthukrishnan *et al.*, 2017; Dimopoulos *et al.*, 2009) when supported by reliable referral pathways into secondary care for more complex treatments. A benefit of the use of dental specialists, and other professionals in a wider MDT, rather than GDPs as the primary care provider, is not evident in the literature.

The eight studies comparing an intervention and control group all reported reduced MRONJ incidence where the preventive strategy was applied. This paper has not sought to compare success rates in MRONJ prevention between different strategies, which in any case would be precluded by several factors in heterogeneous study populations and designs. Besides this, comparison could consider other important factors such as cost or acceptability. Only one study calculated costs, but was a limited analysis of a service in the United States calculating staff wages only, hence is of low applicability to the UK health system (Chang *et al.*, 2017). There will be significant differences in the cost of the different approaches used, and possible issues with availability of dental specialists. Funding any new service has been cited as a problem (Muthukrishnan *et al.*, 2017). Also, only one study assessed the acceptability of the service to patients and clinicians (Muthukrishnan *et al.*, 2017). Over 90% of patients, all CDS dentists, 75% of GDPs and all oncologists were satisfied with the pathway. Therefore, there is scant basis to distinguish between the reports, which might be interpreted as demonstrable alternatives or different options in health service design for this population.

Methods to improve communication, a well-cited problem, were demonstrated in the reports. Muthukrishnan and colleagues (2017) successfully used (leading to 100% being referred) a referral prompt within pharmacy prescribing software. Communication between medical and dental teams was achieved by letter (Vandone *et al.*, 2012, Patel *et al.*, 2015) and a dental referral and assessment form (Tan *et al.*, 2017). If a GDP is to provide pre-drug-treatment dental treatment, communication from the medical team should include the diagnosis, prognosis, planned drug(s) and route of administration (Patel *et al.*, 2011).

Any potential role of the CDS has received little study. The service provides dental care in a range of settings to patients with more complex behavioural or medical needs, physical or learning disabilities. Muthukrishnan and colleagues (2017) showed the effective incorporation of the CDS into an over-arching service, providing care for those who were unable to access mainstream primary care dentistry. Patel *et al.* (2015) used the special care dentistry department in hospital for the same purpose. The only other study utilising GDPs (Dimopoulos *et al.*, 2009) did not comment on provision for those unable to access primary care dentistry.

There were problems with some of the included reports. For the purposes of this paper in gaining details of services, most reports presented incomplete information. In many cases the means of patient recruitment, staffing, range of care provided, means of communication/referral between clinicians and follow-up arrangements were not mentioned or unclear. None reported on the timescales needed to perform the required treatment or if any patients' drug therapy was delayed. Issues were noted with attendance – Catania and colleagues (2016) found 29% of patients declined recall appointments, and Patel *et al.* (2015) found 7 of 93 patients did not attend for their dental assessment. Since adherence rates in trials generally exceed real world scenarios, this represents a potential issue that warrants further study. Most studies were conducted in units allied to oncology centres and thus dealt with high risk patients only. Although the

risk in non-cancer patients is low, their number is very much larger, and this group is poorly represented in the reports identified.

Management of these lower risk patients with osteoporosis is a specific consideration. Guidelines suggest remedial treatment can be as soon as possible after, rather than before, commencing drugs (SDCEP, 2017). The number of patients is large, with many anti-resorptives initiated by GPs. A subgroup comprises older adults admitted acutely to hospital with osteoporotic fractures and commenced on anti-resorptives. It is known dental registration and attendance falls and dental disease burden increases with age. Since dental disease and osteoporosis share some risk factors, this group's dental disease burden may exceed the age-matched average. Problems of cognition, mobility and co-morbidity may affect access to dentistry. However, provision of specific secondary care for dental reviews for such a large group may be unrealistic in a resource-limited healthcare system. Agreements and streamlining of care between GDPs and their hospital and GP colleagues could be helpful, with involvement of the CDS and a smaller specialised hospital service for those with more specific needs. However, this group has received inadequate investigation, thus the optimum arrangement remains unresolved.

This study is the first of its kind and is robust in that all available literature has been reviewed, with a thorough search strategy and no exclusion criteria, so it is likely few relevant studies will have been missed. Despite drawbacks with the existing literature, there is a case for specific access pathways for patients due to commence MRONJ-associated drugs. Overall, a range of services from primary care to hospital, and using dentists and a range of dental and other specialists, have been shown to be effective in preventing MRONJ. The most appropriate strategy in any given area will depend on local/regional conditions within national frameworks, funding and clinician availability. Given the existence in the UK of a universal primary care dental service, improving timely access to this may be more efficient and less costly than creating new, or augmenting existing, hospital dental services. Local hospital/GDP agreements can facilitate quick and predictable access of cancer patients to dentistry when needed, thus circumventing some access difficulties. Employment of a specific oncology coordinator to organise this has been successful (Muthukrishnan *et al.*, 2017). Such agreements could then be transferrable to manage osteoradionecrosis risk in patients planned for jaw radiotherapy as already exist in some areas.

This review has identified gaps in current knowledge. Further research is needed into effective streamlining of GDPs with hospitals and GPs, including patient adherence and satisfaction, and detailed financial analysis, particularly focusing on the different circumstances of low and high risk groups.

Conclusions

MRONJ is drug side effect that can be difficult to treat and causes significant morbidity. Current guidelines advise dental assessment and remedial treatment before initiating MRONJ-associated drugs, but without clear

statement of who should arrange or provide this care, and thus the implication being it be patients and GDPs respectively. This may be appropriate for lower risk patients, but there are potential problems in higher risk cancer patients, and anyone with difficulties accessing dentistry. Various strategies have been studied to address this, mainly hospital-based dental services. In a resource-constrained healthcare system, measures to streamline access to timely primary care GDPs could include specific provision for those unable to do so for various reasons, however more research is needed.

References

- American Association of Oral and Maxillofacial Surgeons. Advisory Task Force on bisphosphonate-related osteonecrosis of the jaws (2007): American Association of Oral and Maxillofacial Surgeons position paper on bisphosphonate-related osteonecrosis of the jaws. *Journal of Oral and Maxillofacial Surgery* **65**, 369-76.
- ADHS (Adult Dental Health Survey) (2009) NHS Digital. Available at <https://digital.nhs.uk/data-and-information/publications/statistical/adult-dental-health-survey/adult-dental-health-survey-2009-summary-report-and-thematic-series>
- Akintoye, S.O. and Hersh, E.V. (2016): Impact of communication between physicians and dentists on the incidence of jaw osteonecrosis caused by bone anti-resorptives *Current Medical Research Opinion* **32**, 1455-56.
- Barker, K., Lowe, D., Olujuhunge, A. and Rogers, S.N. (2007): Survey of members of myeloma UK on bisphosphonate-associated jaw osteonecrosis *British Journal of Haematology* **139**, 626-8.
- Bauer, J.S., Beck, N., Kiefer, J., Stockmann, P., Wichmann, M. and Eitner, S. (2012): Awareness and education of patients receiving bisphosphonates *Journal of Craniomaxillofacial Surgery* **40**, 277-82
- Beth-Tasdogan, N.H., Mayer, B., Hussein, H. and Zolk, O. (2017): Interventions for managing medication-related osteonecrosis of the jaw. *Cochrane Database of Systematic Reviews* Issue 10. Art No CD012432
- Bloor M, Wood F. Keywords in qualitative methods: a vocabulary of research concepts. Sage. 2006
- Bonacina, R., Mariani, U., Villa, F. and Villa, A. (2011): Preventive strategies and clinical implications for bisphosphonate-related osteonecrosis of the jaw: a review of 282 patients. *Journal of the Canadian Dental Association* **77**, b147.
- Bone, H.G., Wagman, R.B., Brandi, M.L., Brown, J.P., Chapurlat, R., Cummings, S.R., Czerwiński, E., Fahrleitner-Pammer, A., Kendler, D.L., Lippuner, K., Reginster, J.Y., Roux, C., Malouf, J., Bradley, M.N., Daizadeh, N.S., Wang, A., Dakin, P., Pannaciuoli, N., Dempster, D.W. and Papapoulos, S. (2017): 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. *Lancet Diabetes Endocrinology* **5**, 513-23.
- Bramati, A., Girelli, S., Farina, G., Dazzani, M.C., Torri, V., Moretti, A., Piva, S., Dimaiuta, M. and La Verde, N. (2015): Prospective, mono-institutional study of the impact of a systematic prevention program on incidence and outcome of osteonecrosis of the jaw in patients treated with bisphosphonates for bone metastases. *Journal of Bone and Mineral Metabolism* **33**, 119-24
- Catania, G., Monaco, F., Limberti, G. Alessio, M., De Martino, I., Barile, C., Fasciolo, A., Baraldi, A., Ladetto, M. and Fusco, V. (2016): Osteonecrosis of the jaws (ONJ) after bisphosphonate treatment in patients with multiple myeloma: decreasing ONJ incidence after adoption of preventive measures. *Dentistry Journal* **4**: E45. doi: 10.3390/dj4040045
- Chang, T.I, Aghazadehsai, N., Hazboun, R., Kawakami, K.K. and Friedlander, A.H. (2017) Preventive dental treatment workload/costs to mitigate antiresorptive bone medication-related osteonecrosis risk. *Oral Health and Preventive Dentistry* **15**, 447-451
- Chen, F. and Pu, F. (2016): Safety of denosumab versus zoledronic acid in patients with bone metastases: a meta-analysis of randomised controlled trials *Journal of Oncology Research and Treatment* **39**, 453-9.
- Dimopoulos, M.A., Kastiris, E., Bamia, C., Melakopoulos, I., Gika, D., Roussou, M., Migkou, M., Eleftherakis-Papaiakovou, E., Christoulas, D., Terpos, E. and Bamias, A. (2009): Reduction of osteonecrosis of the jaw (ONJ) after implementation of preventive measures in patients with multiple myeloma treated with zoledronic acid *Annals of Oncology* **20**,117-20.
- Fedele, S., Porter, S.R., D' Aiuto, F., Aljohani, S., Vescovi, P., Manfredi, M., Arduino, P.G., Broccoletti, R., Musciotto, A., Di Fede, O., Lazarovici, T.S., Campisi, G. and Yarom, N. (2010): Non-exposed variant of bisphosphonate-associated osteonecrosis of the jaw: a case series. *American Journal of Medicine* **123**, 1060-64.
- Green J, Thorogood N. In: Qualitative Methods for Health Research 2nd Ed. Sage. London. Pages 198-203
- Grbic, J.T., Black, D.M., Lyles, K.W., Reid, D.M., Orwoll, E., McClung, M., Bucci-Rechtweg, C. and Su, G. (2010): The incidence of osteonecrosis of the jaw in patients receiving 5 milligrams of zoledronic acid: data from the health outcomes and reduced incidence with zoledronic acid once yearly clinical trials program. *Journal of the American Dental Association* **141**, 136,5-70
- Guarneri, V., Miles, D., Robert, N., Diéras, V., Glaspy, J., Smith, I., Thomssen, C., Biganzoli, L., Taran, T. and Conte, P. (2010): Bevacizumab and osteonecrosis of the jaw: incidence and association with bisphosphonate therapy in three large prospective trials in advanced breast cancer. *Breast Cancer Research and Treatment* **122**,181-8.
- Hellstein, J.W., Adler, R.A. and Edwards, B. (2011): Managing the care of patients receiving antiresorptive therapy for prevention and treatment of osteoporosis. Executive summary of recommendations from the American Dental Association Council on Scientific Affairs *Journal of the American Dental Association* **142**, 1243-51
- Hernlund, E., Svedborn, A., Ivergard, M., Compston, J., Cooper, C., Stenmark, J., McCloskey, E.V., Jönsson, B. and Kanis, J.A. (2013): Osteoporosis in the European Union: medical management, epidemiology and economic burden. A report prepared in collaboration with the International Osteoporosis Foundation (IOF) and the European Federation of Pharmaceutical Industry Associations (EFPIA). *Archives of Osteoporosis* **8**, 136
- Joint Formulary Committee. (2018): *British National Formulary*. 75th ed. London: BMJ Group and Pharmaceutical Press.
- Kim, J-W, Jeong, S-R. and Kim, Y.S. (2016): Perceptions of medical doctors on bisphosphonate-related osteonecrosis of the jaw. *BMC Oral Health* **16**, 92.
- La Verde, N., Bareggi, C., Garassino, M., Borgonovo, K., Sbrulati, P., Pedretti, D., Bianchi, C., Perrone, S., Mihali, D., Cobelli, S., Mantica, C., Rizzo, A. and Farina, G. (2008): Osteonecrosis of the jaw (ONJ) in cancer patients treated with bisphosphonates: how the knowledge of a phenomenon can change its evolution *Supportive Care in Cancer* **16**, 1311-15.
- Migliorati, C.A., Mattos, K. and Palazzolo, M.J. (2010): How patients' lack of knowledge about oral bisphosphonates can interfere with medical and dental care *Journal of the American Dental Association* **141**, 562-6.
- Mücke, T., Deppe, H., Hein, J., Wolff, K.D., Mitchell, D.A., Kesting, M.R., Retz, M., Gschwend, J.E. and Thalgot, M. (2016): Prevention of bisphosphonate-related osteonecrosis of the jaws in patients with prostate cancer treated with zoledronic acid – a prospective study over 6 years *Journal of Craniomaxillofacial Surgery* **44**, 1689-93

- Muthukrishnan, A., Al-Ismail, S., Bertelli, G. and Brown, P. (2017): MRONJ risk reduction pathway – 360 degree survey. *British Dental Journal* **222**, 386-90.
- NHS Digital (2006): *Prescriptions dispensed in the community – statistics for England, 1996-2006*. National Statistics. <https://digital.nhs.uk/data-and-information/publications/statistical/prescriptions-dispensed-in-the-community/prescriptions-dispensed-in-the-community-statistics-for-england-1996-2006>. Accessed 18th August 2019.
- NHS Digital (2018): *NHS Dental Statistics England, 2017-18 – Quarter 3*. <https://files.digital.nhs.uk/34/90F0A0/nhs-dent-stat-eng-17-18-q3-1page.pdf> Accessed 18th August 2019.
- Office for National Statistics. (2015): *Prescriptions dispensed in the community. England 2004-14. Health and social care information team*. <https://files.digital.nhs.uk/publicationimport/pub17xxx/pub17644/pres-disp-com-eng-2004-14-rep.pdf> Accessed 18th August 2019.
- Office for National Statistics. (2016): Cancer registration statistics, England, 2016. Available at <https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancerregistrationstatisticsengland/final2016#cancer-diagnoses-increase-with-age> Accessed 18th August 2019.
- Patel, V., McLeod, N.M.H., Rogers, S.N. and Brennan, P.A. (2011): Bisphosphonate osteonecrosis of the jaw – a literature review of UK policies versus international policies on bisphosphonates, risk factors and prevention. *British Journal of Oral Maxillofacial Surgery* **49**, 251-57.
- Patel, D., Burke, M., Shahabi, Z. and Kerr, B. (2015): A service review investigating dental extractions in a specialist screening clinic before intravenous bisphosphonates for patients with cancer. *Journal of Disability and Oral Health* **16**, 54–58.
- Poxleitner, P., Engelhardt, M., Schmeleisen, R. and Voss, P. (2017): The prevention of medication-related osteonecrosis of the jaw. *Deutsches Arzteblatt* **114**, 63-9.
- Ripamonti, C.I., Maniezzo, M., Campa, T. and Maniezzo, N. (2009): Decreased occurrence of osteonecrosis of the jaw after implementation of dental preventive measures in solid tumour patients with bone metastases treated with bisphosphonates. The experience of the National Cancer Institute of Milan. *Annals of Oncology* **20**, 137-45.
- Rogers, S.N., Palmer, N.O., Lowe, D. and Randall, C. (2015): United Kingdom nationwide study of avascular necrosis of the jaws including bisphosphonate-related necrosis. *British Journal of Oral Maxillofacial Surgery* **53**, 176-82.
- Ruggiero, S.L., Dodson, T.B., Fantasia, J., Goodday, R., Aghaloo, T., Mehrotra, B., and O’Ryan, F. (2014): American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw - 2014 update. *Journal of Oral and Maxillofacial Surgery* **72**, 1938-56.
- Sim, le-W., Sanders, K.M., Borromeo, G.L., Seymour, J.F. and Ebeling, J.R. (2015): Declining incidence of medication-related osteonecrosis of the jaw in patients with cancer. *Journal of Clinical Endocrinology and Metabolism* **100**, 3887-93.
- Scottish Dental Clinical Effectiveness Programme (2017): *Oral health management of patients at risk of medication-related osteonecrosis of the jaw*. NHS Education for Scotland
- Steele, J.G. (2009): *NHS dental services in England – an independent review*. London: DH Publications.
- Sturrock, A., Preshaw, P.M., Hayes, C. and Wilkes, S. (2017): Attitudes and perceptions of PGs and community pharmacists towards their role in the prevention of bisphosphonate-related osteonecrosis of the jaw: a qualitative study in the north east of England. *BMJ Open* **7**, 9.
- Taguchi, A., Shiraki, M., Sugimoto, T., Ohta, H., and Soen, S. (2016): Lack of cooperation between physicians and dentists during osteoporosis treatment may increase fractures and osteonecrosis of the jaw. *Current Medical Research and Opinion* **7**, 1261-8.
- Tan, Y. and Barrett, S. (2017): Bisphosphonate-associated osteonecrosis of the jaw (BONJ) in metastatic breast cancer patients in Greater Glasgow and Clyde. *Clinical Oncology* **29**, e95-104.
- Tanna, N., Steel, C. and Stagnell, S. (2017a): Awareness of medication-related osteonecrosis of the jaw amongst dentists and doctors in the UK. *Oral Surgery, Oral Medicine, Oral Pathology, Oral Radiology* **124**, e193.
- Tanna, N., Steel, C., Stagnell, S. and Bailey, E. (2017b): Awareness of medication-related osteonecrosis of the jaw (MRONJ) amongst general dental practitioners. *British Dental Journal* **222**, 121-125.
- Taylor, T., Bryant, C. and Popat, S. (2013): A study of 225 patients on bisphosphonates presenting to the bisphosphonate clinic at King’s College Hospital. *British Dental Journal* **214**, E18.
- Vaismoradi M, Turunen H, and Bondas T. Content analysis and thematic analysis: implications for conducting a qualitative descriptive study. *Nursing & Health Sci* 2013 **15**, 98-405
- Vandone, A.M., Donadio, M., Mozzati, M., Ardine, M., Polimeni, M.A., Beatrice, S., Ciuffreda, L. and Scoletta, M. (2012): Impact of dental care in the prevention of bisphosphonate-associated osteonecrosis of the jaw: a single-center clinical experience *Annals of Oncology* **23**, 193-200.