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Case series of medication-related osteonecrosis of the jaw (MRONJ) patients prescribed a drug holiday

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Abstract

The role of a drug holiday in the management of medication-related osteonecrosis of the jaw (MRONJ) remains controversial. Current UK guidance does not recommend this practice given the lack of conclusive evidence, and potential risk of skeletal-related events or cancer metastasis. This paper aims to describe a series of fifty patients with confirmed MRONJ who were prescribed a drug holiday as part of their management. Data were collected on exposures including: anti-resorptive and/or anti-angiogenic drug history, duration of drug, method of administration, concurrent therapy, MRONJ stage, management of MRONJ and duration of drug holiday. The primary outcome was complete healing as documented in the clinical notes. Multivariate Cox regression analysis was performed to evaluate the association between exposures and primary MRONJ outcome. Models were adjusted for age, sex, and index of multiple deprivation. Survival analysis was performed using a log-rank test, censoring any patients with no primary outcome recorded ($p < 0.05$). A total of 44% of patients stopped their medication for >36 months. Over half of all MRONJ cases presented in the posterior mandible and dental extraction was the most common precipitating factor (76%). Almost three-quarters (72%) of patients achieved complete healing. MRONJ recurrence (new site) was reported at 30%, mainly in those with incomplete healing of the initial area. There was a lack of evidence for an association between all recorded exposures and the primary MRONJ outcome using multivariate Cox regression. Similarly, we did not demonstrate evidence for an association between the duration of the drug holiday and MRONJ outcome. Our results support published guidelines, which do not recommend the discontinuation of bone modifying drugs for the prevention of MRONJ, or as part of treatment for established MRONJ.

Keywords: Medication-related osteonecrosis of the jaw; MRONJ; Bisphosphonates; Drug Holiday

Introduction

Medication-related osteonecrosis of the jaw (MRONJ) is a rare, but debilitating condition which can occur in patients exposed to anti-resorptive and anti-angiogenic medications used in the treatment of common diseases, including osteoporosis and breast cancer. The first case of osteonecrosis of the jaw was linked to bisphosphonate therapy.[1] Since then, there have been increasing reports of MRONJ in patients taking a range of other anti-resorptive and anti-angiogenic medications.[2–4] The incidence of MRONJ is around 1% in cancer patients and 0.1% in those with other metabolic bone diseases, such as osteoporosis.[5,6] Given that MRONJ is a rare, multifactorial condition, it has been difficult to study. Risk factors include recent dentoalveolar surgery (or any surgical procedure involving bone), mucosal trauma (such as from poor fitting dentures), smoking and untreated dental or periodontal disease.[7–9] High-risk patients have been identified as those treated with oral or intravenous bisphosphonates for >5 years, those taking anti-resorptive or anti-angiogenic drugs for any length of time alongside systemic steroids, oncology patients, and those with a previous MRONJ diagnosis.[5]

MRONJ is a chronic and potentially progressive disease, therefore management of the condition remains a challenge. Multiple comorbidities commonly confound the older popu-

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lation of interest, so the impact of any intervention can be difficult to interpret.[10] A recent American Association of Oral and Maxillofacial Surgeons (AAOMS) position paper recommends both non-operative (conservative management, with or without removal of mobile sequestra) and operative (resection) management strategies.[11] Given the difficulty in successfully treating MRONJ, there has been a move towards prevention, with best practice recommending education, reinforcement of oral hygiene, dental screening, and surgery prior to commencing therapy.[6] While early studies suggested prophylactic drug holidays may be beneficial,[12] current UK guidance does not recommend this practice given the lack of conclusive evidence, and potential risk of skeletal-related events or cancer metastasis.[5,6] However, the administration of drugs associated with MRONJ may still be deferred or discontinued at the discretion of the prescribing physician, as part of a shared-decision making process with the patient on a case-by-case basis.[6,11,13] A systematic review on the efficacy of a drug holiday to reduce the risk of MRONJ highlighted the need for more evidence.[14]

This paper aims to describe a case series of confirmed MRONJ patients at a single UK institution who experienced a drug holiday following discussion with their prescribing physician. We performed multivariate analysis to determine the association between exposures and time to complete healing, as a primary outcome.

Methods

A case series of 50 patients were recruited with an established diagnosis of MRONJ. Patients presented to a single UK dental hospital from 2014–2019, referred from their general dental/ medical practitioner, or via internal referral. Information for this study was obtained retrospectively from a local secure electronic hospital database, which logged the MRONJ cases and further detail on pre-defined exposures and outcomes were extracted using their clinical notes. At the time of presentation, a detailed history and diagnosis of MRONJ was confirmed, with staging (as defined in **Supplementary Table 1, online only**). All drug holidays were prescribed by the relevant practitioners (such as rheumatologists/oncologists). Some patients had already commenced a drug holiday prior to attending the dental hospital on the advice of other practitioners and some drug holidays were requested following baseline examination. These drug holiday periods were recorded as the number of months the patient had discontinued the drug for. Patients were then followed up over time, with healing documented as either complete or incomplete as part of follow-up clinical review. All individual patient data was anonymised and is presented only as summary statistics here.

Exposures were defined as:

- Previous exposure to anti-resorptive and/or anti-angiogenic drug for any disease, with a presentation of MRONJ
- Duration of exposure to the drug and method of administration (oral or intravenous)
- Any concurrent therapy and its duration such as corticosteroids or methotrexate
- MRONJ stage at presentation
- Non-operative or operative management of MRONJ
- Duration of drug holiday prior to MRONJ management

Primary outcome was defined as:

- Complete or incomplete healing as documented by a clinician on review in the clinical notes

Secondary outcome was defined as:

- Any MRONJ recurrence at a new, separate site

The data collected from clinical notes for each patient identified in the local secure electronic hospital database included: sex, age at diagnosis, ethnicity, index of multiple deprivation (IMD) score based on postcode, anti-resorptive and/or anti-angiogenic drug exposure, reason for treatment and duration of treatment, method of drug administration (oral or intravenous), any concurrent therapies, any medical comorbidities, previous history of MRONJ, MRONJ stage and site, suspected cause of MRONJ, drug holiday duration, management of MRONJ, outcome (such as complete healing or incomplete healing), time to outcome and disease recurrence at a separate site.

Statistical analysis

Continuous variables were described using mean and standard deviations. Categorical variables were described using counts and percentages. Multivariate Cox regression analysis to evaluate the association between exposures and primary MRONJ outcome was performed in Stata (StataCorp, version 16.1) using the *stcox* function. Models were adjusted for age, sex and IMD. Survival (time-to-event) analysis was performed in Stata (StataCorp, version 16.1) using a log-rank test (*sts test* function), censoring any patients with no primary outcome recorded. The null hypothesis for this test assumes that there is equality of the survivor function across each group. All p values were two-sided, with a critical significance threshold set at <0.05. This was interpreted alongside the Chi squared (χ^2) test statistic. Kaplan–Meier curves were generated using the *stcurve* function in Stata (StataCorp, version 16.1).

Results

Baseline characteristics

In total, 50 patients who all experienced a drug holiday during their management of MRONJ were identified, with a mean age of 75. The mean (SD) prospective follow-up period was 20 (13) months. The majority were female (82%) and white (British) (98%). There was no clear trend evident across index of multiple deprivation (IMD) quintiles, with

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the highest number of cases reported in quintile 1 (least deprived) (30%), followed by quintiles 2 (26%) and 4 (26%). Almost one-third (28%) had an associated medical comorbidity.

Half of the cases were diagnosed with stage 2 MRONJ (**Supplementary Table 1, online only**) on presentation, followed by 34% as stage 1, 12% as stage 3, and only 4% as stage 0 (Table 1). Over half (56%) of all MRONJ presentations were in the posterior mandible. Almost all patients (n = 48) reported multiple signs and symptoms, the most common being pain, swelling, or discharge of pus. The most commonly reported procedure associated with MRONJ diagnosis was a recent dental extraction (76%), with remaining cases described as spontaneous or of unknown aetiology.

Drug exposures and duration

Over half (56%) of the MRONJ case series reported a history of taking bisphosphonate drugs, followed by 18% who had experienced monoclonal antibody therapy, and only 2% who had taken anti-angiogenic drugs (Table 2). The only indications for patients being prescribed these medications in this study was for osteoporosis (56%) and cancer (44%), respectively. The duration of exposure ranged from eight months to 15 years, with the majority (48%) taking their medication for less than five years (Table 2). The most common method of drug administration was intravenous (50%), with over a third (34%) administering orally and 16% experiencing a combination of both. Over one-third (38%) of patients reported taking concurrent medications including steroids or methotrexate (Table 2).

Drug holiday duration and MRONJ outcomes

With respect to drug holidays, 44% of the patients had their medication stopped for >36 months following review by their prescribing physician. A further 28% had their therapy discontinued for 13–36 months, with 14% for <12 months

Table 1
Baseline characteristics of medication related osteonecrosis of the jaws (MRONJ) case series Data are No. (%).

Patient characteristics	Total MRONJ cases(n = 50)
Sex:	
Female	41 (82)
Male	9 (18)
Age at diagnosis:	
40-49	2 (4)
50-59	2 (4)
60-69	11 (22)
70-79	13 (26)
80+	22 (40)
Ethnicity:	
White (British)	49 (98)
Black Caribbean	1 (2)
IMD score (quintiles)	
1	15 (30)
2	13 (26)
3	2 (4)
4	13 (26)
5	7 (14)
Medical comorbidity *	
No	36 (72)
Yes	14 (28)
MRONJ stage:	
Stage 0	2 (4)
Stage 1	17 (34)
Stage 2	25 (50)
Stage 3	6 (12)
MRONJ site:	
Posterior mandible	28 (56)
Anterior mandible	6 (12)
Posterior maxilla	10 (20)
Anterior maxilla	5 (10)
Combination of maxilla and mandible	1 (2)

Key: IMD, index of multiple deprivation quintiles (1 = least deprived; 5 = most deprived); * Medical comorbidity included smoking, diabetes mellitus, rheumatoid arthritis, hypocalcaemia, hyperparathyroidism, vitamin D deficiency, osteomalacia, renal dialysis, and anaemia.

Table 2
Description of medication related osteonecrosis of the jaws (MRONJ) exposures and outcomes. Data are No. (%).

Variables	Total MRONJ cases (n = 50)
Drug type:	
Bisphosphonate	28 (56)
Monoclonal antibody	9 (18)
Anti-angiogenic	1 (2)
Combination therapy	12 (24)
Reason for treatment:	
Osteoporosis	28 (56)
Cancer	22 (44)
Duration of therapy:	
<5 years	24 (48)
5–10 years	16 (32)
>10 years	3 (6)
Unknown duration	7 (14)
Method of administration:	
Oral	17 (34)
Intravenous	25 (50)
Combination therapy	8 (16)
Concurrent therapy: *	
No	32 (62)
Yes	19 (38)
Duration of drug holiday:	
Discontinued for ≤12 months	7 (14)
Discontinued for 13–36 months	14 (28)
Discontinued for >36 months	22 (44)
Missing data	7 (14)
MRONJ (separate site) recurrence:	
No	35 (70)
Yes	15 (30)
MRONJ management:	
Conservative alone	40 (80)
Conservative + removal of mobile sequestra	10 (20)
Operative (resection)	0 (0)
Outcomes:	
Incomplete healing (improvement)	14 (28)
Complete healing	36 (72)

Key: * Concurrent therapy included steroids and methotrexate taken by the patient.

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Table 3
Multivariate analysis of association between exposures and medication related osteonecrosis of the jaws (MRONJ) primary outcome.

Exposure	Unadjusted analysis			Adjusted analysis*		
	HR	95% CI	p value	HR	95% CI	p value
MRONJ stage:						
0	Ref				Ref	
1	0.51	0.38 to 6.93	0.62	0.47	0.03 to 7.66	0.60
2	1.07	0.13 to 9.08	0.95	0.83	0.03 to 24.87	0.92
3	0.42	0.37 to 4.61	0.47	0.58	0.04 to 9.49	0.70
Site:						
Maxilla (ref) vs mandible	1.17	0.39 to 3.54	0.78	1.09	0.34 to.51	0.88
Drug type:						
Bisphosphonate (ref) vs monoclonal antibody	2.50	0.45 to 14.00	0.30	3.10	0.17 to 55.64	0.44
Reason for treatment:						
Osteoporosis (ref) vs oncology	2.24	0.66 to 7.57	0.20	1.51	0.38 to 6.07	0.56
Duration of therapy:						
<5 years (ref) vs 5–10 years	1.85	0.35 to 9.71	0.47	2.41	0.22 to 26.36	0.47
Method of administration:						
Oral (ref) vs intravenous	1.53	0.41 to 5.73	0.53	0.41	0.45 to 3.62	0.42
Medical comorbidity:						
No (ref) vs yes	0.65	0.19 to 2.16	0.48	0.44	0.10 to 1.92	0.27
Concurrent therapy:						
Yes (ref) vs no	1.66	0.49 to 5.63	0.42	2.29	0.40 to 13.17	0.35
Drug holiday duration:						
Continuous (months)	1.02	1.00 to 1.05	0.07	1.05	1.00 to 1.08	0.05
MRONJ management:						
Conservative management alone (ref) vs conservative + removal of mobile sequestra	2.05	0.59 to 7.15	0.26	1.75	0.34 to 8.85	0.50

Key: * Adjusted for age, sex, and Index of Multiple Deprivation (IMD).

(Table 2). No skeletally-related events, outcomes of cancer progression, or other complications were reported during the study period.

Almost three-quarters (72%) were documented to have complete healing following clinical review, with 28% experiencing incomplete healing. MRONJ (new site) recurrence was reported at 30%, which was almost all in those with incomplete healing of the initial site (Table 2 and **Supplementary Table 2, online only**). The majority of cases (80%) received non-operative conservative management alone, with 20% requiring adjunctive removal of mobile sequestra. No patients in this case series required resection. Over half (54%) of those treated with conservative management alone resulted in complete healing, with no recurrence of MRONJ in a new site.

There was a lack of evidence for an association between recorded exposures and the primary MRONJ outcome using multivariate Cox regression (Table 3). In general, the associations attenuated further with adjustment for age, sex, and IMD. Kaplan–Meier curve analysis demonstrated a longer median survival time to complete healing for those who had conservative management alone (39 months), versus those who had conservative management with adjunctive removal of mobile sequestra (31 months). However, this was not found to be significantly different following a log-rank test ($\chi^2 = 0.29$, $p = 0.59$) (Fig.1). Similarly, there was no difference between drug holiday duration groups ($\leq$12 months, 13–36 months, >36 months) using a log-rank test ($\chi^2 = 0.37$, $p = 0.83$).

Discussion

In this study, we present the outcomes for 50 MRONJ patients who experienced a drug holiday. Baseline characteristics were in keeping with those previously described as at risk of MRONJ, such as the majority being older females, with affected sites in the posterior mandible, linked to higher rates of intravenous drug administration. Almost three-quarters (72%) were documented to have complete healing, mostly using conservative management alone. While MRONJ (new site) recurrence was reported at 30%, this was found mainly in those with incomplete healing of the initial area. Despite a lack of evidence for association between a wide range of exposures and complete healing, response to treatment may also be as a result of genetic predisposition or other environmental exposures not measured in this study.[15,16] Furthermore, wide confidence intervals suggest a lack of precision in our data, possibly as a result of the small sample size.

Bisphosphonates have a high affinity to bind with hydroxyapatite crystals in bone, inhibiting osteoclastic resorption. However, drug elimination is complex, with three different half-lives previously described.[17] The most rapid half-life effects drug concentration in the soft tissues, with the intermediate half-life reducing in drugs bound at the surface of bone. The longest half-life impacts the internal skeleton, as the drug is buried during new bone formation and therefore may not be released for decades.[10,17] Discounting drug holidays principally due to these longer half-lives, may mean we

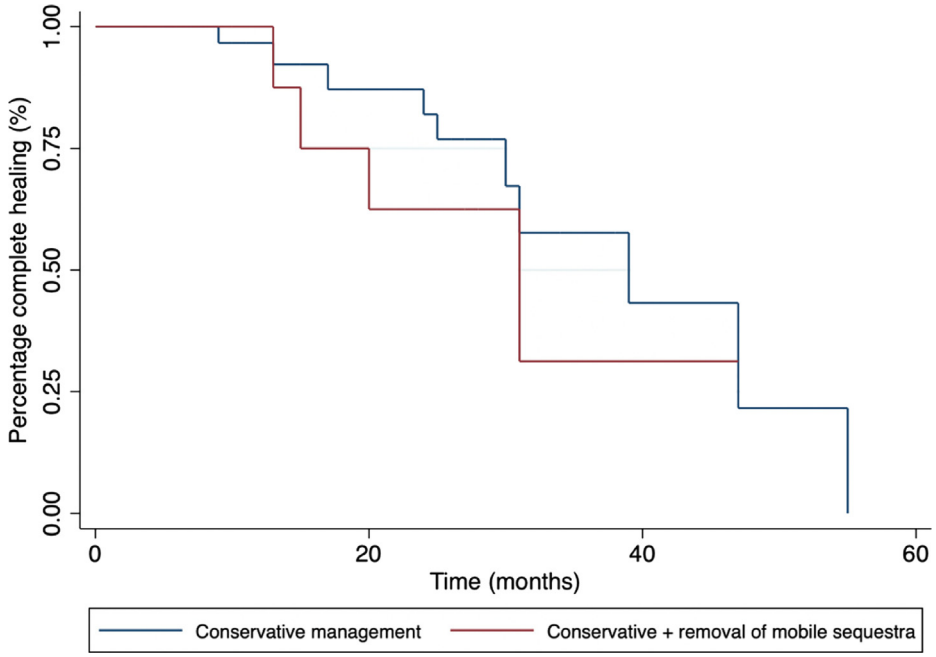

Figure 1. Kaplan–Meier curves for MRONJ primary outcome, by management and drug holiday duration.

miss the potential benefit of rapid and intermediate elimination effects on both the soft tissues and on osteoclasts at the bony surface. In general, drug holidays remain controversial in the management of MRONJ, with limited evidence for their effectiveness. Several retrospective and *in vitro* studies have reported beneficial effects of a drug holiday in achieving complete healing.[18–21] A systematic review and meta-analysis of 13 studies concluded that a drug holiday protocol promotes complete healing after oral surgery procedures.[22] Conversely, other retrospective studies have failed to demonstrate the benefit of a drug holiday,[23–25] with most recommending discontinuation on a case-by-case basis.[26–29] Using multivariate regression analysis, we failed to demonstrate an association between drug holiday duration (of varying length of time) and MRONJ outcome. Our result therefore supports the AAOMS,[11] as well as SDCEP[5] and Royal College of Physicians[6] guidelines, which do not recommend the discontinuation of bone modifying drugs.

This study has a number of limitations, including a small sample size which could reduce power to detect associations and potential selection bias, as patients were entered into the electronic hospital database by the treating clinician rather than randomly or consecutively sampled. As all of the aforementioned publications emerged during the course of our study, this could have changed those cases selected for a drug holiday, or the duration of prescribed drug holidays. Data were only collected from a single UK institution, with participants mainly white (British), with stage 1 or 2 disease complexity, therefore reducing the generalisability of the results. Data were extracted from clinical notes, so there is a risk of inaccurate recording or missing data. This was the case for duration of drug holiday data, which was missing for 14% of cases, for example because start time was not documented in the notes, or if the patient could not recall the time when the drug holiday was initiated by another practitioner prior to attending the dental hospital. There was also variability in the duration of drug holidays prescribed by various physicians, making it difficult to recommend any one protocol. Finally, this analysis informs us about associations only between variables, not causal effects. Larger studies, with a prospective or trial design and longer follow up would be required to establish causal effects between drug holidays and MRONJ outcomes. However, with current guidance this is likely to be only in a small number of appropriate cases, where the prescribing clinician believes there to be a substantial benefit which outweighs any risks.

Conclusion

The results from this small retrospective case series support published guidelines, which do not recommend the discontinuation of bone modifying drugs for the prevention of MRONJ, or as part of treatment for established MRONJ.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement/confirmation of patient permission

Not applicable - anonymised summary retrospective data used only

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Appendix A. Supplementary material

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