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Medication-related osteonecrosis of the jaw –analysing the range of implicated drugs from the Australian Database of Adverse Event Notifications

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Principle investigator statement:

The authors confirm that the PI for this paper is Leanne Teoh and that she has direct responsibility for the extraction of the data.

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Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon but potentially debilitating condition characterised by non-healing jaw bone, associated with bisphosphonates and denosumab. A growing range of other drugs, such as anti-resorptives, are implicated.

What this study adds:

This study contributes to the sparse but growing literature associating an increasing number of drugs with MRONJ. This highlights the importance of considering all possible drugs that elevate a patient's MRONJ risk.

Abstract

Background and aims: Medication-related osteonecrosis of the jaw (MRONJ) is an uncommon but potentially debilitating condition, characterised by non-healing jaw bone, with or without mucosal exposure, in the presence of certain drugs. Those already strongly associated with MRONJ include anti-resorptives denosumab and bisphosphonates, however a growing range of other non-antiresorptive drugs are implicated. The aim of this study was to analyse all case reports of MRONJ submitted to the publicly-available Database of Adverse Event Notification (DAEN) from the Therapeutic Goods Administration (TGA) in Australia.

Methods: The TGA was contacted on 6 January 2020 and asked for all reports containing the words "osteonecrosis of the jaw". This was provided in a spreadsheet of de-identified reports received from commencement of the database in 1971 until 1 October 2019.

Results: The drugs implicated in the 419 cases were divided by established drugs with MRONJ and secondary drugs that possibly contribute to MRONJ development. While the majority of cases were associated with denosumab or bisphosphonates (n=405), there were 14 reports where secondary agents that directly or indirectly affect bone turnover, were also implicated. Some of these secondary drugs, including adalimumab, etanercept, methotrexate and rituximab have previously been associated with MRONJ in published case reports.

Conclusions: This study contributes to the sparse but growing literature associating an increasing number of drugs with MRONJ, and underscores the importance of considering all possible drugs that elevate a patient's MRONJ risk.

Keywords: Drug information, adverse drug reactions, medication safety

Introduction

Medication related osteonecrosis of the jaw (MRONJ) has been described as a condition where exposed bone is detected through an intraoral or extraoral fistula/e in the maxillofacial region, does not heal within 8 weeks and occurring in a patient who has received a bone-modifying agent (BMA) or an angiogenesis inhibitor, with no history of head and neck radiation.[1] Since the first publication describing MRONJ by Marx in 2003,[2] an increasing range of drugs have been associated with this relatively rare but serious condition. Worryingly, in the last two decades, there has been a steady increase in its incidence despite the potential for under-reporting, particularly with newly implicated medications and the diagnosis of MRONJ in the absence of a mucosal defect.[3, 4] Appropriate recognition of risk factors and implicated drugs are critical for obtaining informed consent and early diagnosis is imperative for improving patient prognosis.

While many theories exist on the mechanism for MRONJ, its exact pathophysiology is unknown. Current theories centre on five main ideas: inhibition of bone remodelling, infection and inflammation, a lack of immune resilience, soft tissue toxicity and impaired angiogenesis.[5]

The most common trigger for MRONJ is an invasive dental procedure, with extractions being the most frequently implicated.[1] In an Australian study, dental extractions were the precipitating factor in 73% of cases of MRONJ associated with bisphosphonate use.[6] McGowan et al found tooth removal was the most common precipitating factor for MRONJ in patients taking antiresorptive drugs.[7] However, Filleul et al found up to 26% of cases may have no identifiable predisposing risk factor.[8] Other risk factors include invasive dental procedures such as implant placement and periodontal surgery, as well as ill-fitting dentures, systemic ill-health, and concomitant oral disease such as periodontitis and periapical abscesses.[1, 7, 9]

Immune compromise has been implicated as a contributor in the aetiology of MRONJ. Use of systemic glucocorticosteroids has also been associated with increased risk.[1] However, their impact is unlikely due to immunosuppression alone since haematological evidence of

diminished immune function was not found to be predictive of MRONJ risk.[10] Much focus in the literature has been on the biomarker of bone resorption, C-terminal telopeptide (CTX) as a marker of bisphosphonate-related MRONJ risk. However, a systematic review and meta-analysis has shown CTX not to be an accurate predictor of MRONJ.[10, 11]

Certain medical conditions have been shown to be associated with increased risk of MRONJ. Patients with multiple myeloma, breast cancer, prostate cancer and renal cancer have a higher incidence of MRONJ compared with non-cancer patients exposed to the same antiresorptive agents, but this is likely due to the higher doses and more frequent administration used when treating cancer.[7, 9, 12, 13] The incidence of MRONJ associated with bisphosphonates or denosumab use in cancer patients is between 1-15%, and for patients with osteoporosis it is estimated at 1 in 10,000 and 1 in 100,000 per year of use.[12] A case-control study showed that systemic comorbidities and polypharmacy of any kind again increased risk of MRONJ.[14]

While it is well-documented that MRONJ is associated with bisphosphonates and denosumab, there are a growing number of MRONJ case reports associated with other medications, including antiangiogenic agents.[1, 15, 16] This is mostly due to two reasons as stated by Fusco and colleagues:[17]

1. These osteonecrosis of the jaw (ONJ) patients have not been treated with BPs or denosumab.
2. An increase in cases of ONJ in cancer patients undergoing treatment, which included bisphosphonates (BPs) (or denosumab) and the new suspected drugs.

The American Association of Oral and Maxillofacial Surgery position paper documented bevacizumab, sirolimus, sorafenib and sunitinib[1], while the 2015 International Taskforce on Osteonecrosis of the Jaw did not support this due to insufficient evidence,[7, 12] most likely because these drugs had only been in clinical use for a decade at that time. The aim of the present analysis was to summarise and describe all the case reports of MRONJ submitted to the Australian Database of Adverse Event Notifications (DAEN) between 1971 and October 2019.[18]

Method

The Therapeutic Goods Administration (TGA) in Australia maintains the DAEN, which is a publicly available database of adverse drug reaction (ADR) reports. The DAEN contains reports of suspected adverse drug reactions notified by members of the public, health professionals and the medicines industry in Australia.[18] Submission of these reports are voluntary and relies on goodwill, and therefore does not represent the total number of cases that exist or have been identified. As these data can only ever represent the "tip of the iceberg", they are used for "signal detection" to determine when a safety issue may be associated with certain medications.

The TGA was contacted on 6 January 2020 and asked for all reports containing the words "osteonecrosis of the jaw". This was provided in a spreadsheet of abbreviated reports received from commencement of the database in 1971 until 1 October 2019, which was the most recent date possible due to the TGA's standard 3-month processing delay. The first reported occurrence of MRONJ on this database was in 2005. To ensure all possible cases of MRONJ were included, on the 7 September 2020 the TGA was contacted again and asked for all reports containing the words "mandible", "maxilla, "jawbone", for which there were no extra reports.

Data for each subject included the TGA-identifying case number, patient's gender (male, female or unspecified), date of each report, patient's age, if the adverse effect (MRONJ) had resolved/was ongoing, the suspected medicine(s) and concurrent medicines. All data was de-identified on receipt, and case numbers removed.

The TGA data assigns a drug as the suspected causative agent, of which there may be more than one. Other medicines are listed as "concurrent" medicines. This data was then re-arranged into two columns to show cases specific to each drug. The "primary column" showed reports associating established drugs implicated with MRONJ as reported in the AAOMS position paper,[1] including denosumab, bisphosphonates (alendronate, risedronate, pamidronate and zoledronic acid), and bevacizumab, sirolimus, sorafenib and sunitinib.

However, there may have been other drugs that contributed to each case's MRONJ risk from the "concurrent medicines". Therefore, another column entitled "secondary drugs" was added to the analysis. To do this, the authors used their knowledge and experience as to which drugs from the "concurrent" medicines were most likely to contribute to development of MRONJ. These secondary medicines have direct or indirect effects on bone remodelling, have previously been reported to be associated with MRONJ, and/or are associated with immune compromise or impaired healing. The suspected causative agents assigned by the TGA were included.

Results

The DAEN database identified 419 reported cases of MRONJ with the date of the first report being 15 November 2005. The cases involved 86 male patients and 245 female patients, with gender not specified in 88 cases.

MRONJ reported with denosumab

Denosumab was the sole suspected agent in 221 cases, with a further 20 cases reported where denosumab was listed in addition to other suspected medications, including prednisolone (7 cases), docetaxel (3 cases), letrozole (3 cases) and leuprorelin (3 cases). Females accounted for the majority of cases (131), with males at 37 cases, and 73 cases where gender was not specified.

MRONJ reported with bisphosphonates

The total number of reports involving bisphosphonates (alendronate, pamidronate, risedronate and zoledronic acid) totalled 163 reports.

Zoledronic acid accounted for the most cases; 54 reports were listed with zoledronic acid as a sole suspected agent, for the remaining 12 cases zoledronic acid was reported in conjunction

with several possible secondary agents, including cyclophosphamide (3 reports), bortezomib (2 reports) and dexamethasone (2 reports).

Alendronate and risedronate cases totalled to 61 and 18 reports respectively, with only 4 cases and 2 cases respectively also reporting prednisolone as a possible suspected contributing agent to the development of MRONJ.

Pamidronate was reported in 5 cases, predominately in males (4 reports), and with one report also listing thalidomide as another suspected contributing agent.

Other drugs implicated with MRONJ used in conjunction with anti-resorptive agents

The most common medications without anti-resorptive properties taken concurrently with either denosumab or bisphosphonates and potentially implicated with MRONJ were the glucocorticoids dexamethasone (5 reports) and prednisolone (18 reports), as well as the antineoplastic drugs: cyclophosphamide (7 reports), docetaxel (5 reports), lenalidomide (5 reports) and thalidomide (5 reports).

MRONJ reported without anti-resorptive agents

Cases not including an antiresorptive agent accounted for 14 reports. The most common drugs that may be associated with MRONJ included adalimumab (3 reports), lenalidomide (2 reports), teriparatide (2 reports). (Table 1)

These cases are all documented in Table 1. More than one suspected drug could have been documented per case report.

Table 2 summarises all the possible secondary drugs that may have contributed to the development of MRONJ.

Discussion

This analysis of the Australian adverse events database, the DAEN, shows that during the 14-year period (2005 to 2019), while the majority of MRONJ cases were associated with denosumab or bisphosphonates, there were various other medications possibly implicated that have not been previously identified in the literature. In addition, this retrospective analysis shows that immunosuppressants and anti-angiogenic drugs such as adalimumab, thalidomide and lenalidomide may have been associated with some of these cases. As MRONJ is a relatively rare condition and its pathophysiology is still unknown, this analysis highlights the importance of considering all drugs that may be implicated with MRONJ.

MRONJ is a well-established adverse effect of denosumab and the results presented here show that this medication was the most reported in the DAEN. Longer treatment duration and higher doses have been correlated with an increased risk of MRONJ.[19, 20] Given that bisphosphonates have been in widespread use prior to denosumab, it is possible that some patients have been treated with a bisphosphonate prior to denosumab, but this was not documented or asked of the patient. It is already established that a history of bisphosphonate use increases ONJ risk.[1, 13]

Bisphosphonates were the first drug class to be associated with MRONJ and were associated in 160 case reports in the present study. Nevertheless, the exact pathophysiology is unknown with proposed theories include altered bone remodelling, inhibition of osteoclast differentiation and angiogenesis inhibition.[1] The increased rate of bone remodelling in the jaw is also proposed as to why MRONJ occurs mostly exclusively in the jaws only,[1] although a case report has associated bisphosphonates with osteonecrosis of the external auditory canal.[21] The potency and duration of the bisphosphonate affects risk, with intravenous bisphosphonates at higher doses used for oncology having a greater incidence than oral bisphosphonates used for osteoporosis.

The AAOMS white paper listed antiangiogenic drugs in addition to antiresorptive drugs as being associated with MRONJ,[1] and there have been increasing case reports of their association.[15, 22, 23] The proposed mechanism is the inhibition of blood vessel growth that occurs after procedures such as extractions.[1] The prevalence of MRONJ related to

antiangiogenic agents will also likely be influenced by the pathophysiology of the malignancies that require antiangiogenic therapy, confounded by the complex combinations of medications used to treat these conditions.[15] Several drugs of varying classes possess anti-angiogenic properties as identified in the DAEN.

The mammalian target of rapamycin (mTOR) inhibitors (e.g. everolimus, sirolimus, temsirolimus) has antiangiogenic effects due to the prevention of cytokine B and T-cell induced proliferation and some are associated with MRONJ.[15, 24] Everolimus was associated with 3 cases of MRONJ reported here in the DAEN. This mTOR inhibitor has had several case reports in association with MRONJ: alone, with immunosuppressants, with bisphosphonates and with denosumab.[25-27] Underscoring this association, thalidomide and lenalidomide which also inhibit vasculogenesis[24, 28] were identified in the DAEN as a possible confounder in the present study.

Adalimumab, the tumour necrosis factor (TNF) alpha inhibitor, was reported in 3 cases in the DAEN. TNF alpha has positive effects on systemic bone loss in rheumatoid arthritis as it has effects to increase osteoclast activity and osteoblast production, thereby producing a decreased effect on bone turnover.[29] Case reports implicating adalimumab postulate that these biologic agents may compromise oral healing by causing a reduction in RANKL leading to a reduction in osteoclasts, or impeding bone repair due to their apoptotic effect on monocytes.[30, 31] Furthermore, the well documented adverse effect of infections due to adalimumab-induced immunosuppression may contribute to the pathogenesis of MRONJ.[30]

Although no tyrosine kinase inhibitors were listed in this database, they are an emerging drug class with anti-angiogenic properties that is associated with MRONJ. Several drugs such as sorafenib, sunitinib, cabozantanib and pazopanib have several case reports associated with MRONJ.[15, 23, 32] A case report also exists for axitinib.[33] In addition, the human epidermal growth factor receptor 2 antagonists, trastuzumab and pertuzumab, with anti-angiogenic properties has had case reports in association with MRONJ.[34, 35] Bortezomib, a proteasome inhibitor, was reported in this study.

It has been reported in the AAOMS paper and the International Taskforce on ONJ that the use of glucocorticoids are a confounding variable that can increase a patient's risk of MRONJ, due to their well-documented effects on bone, including inhibition of wound formation in bone and soft tissue, and increased apoptosis of osteoblasts and osteocytes.[36, 37] Dexamethasone, prednisolone, mycophenolate and cyclophosphamide were all listed as concurrent medications in the DAEN, as well as cytotoxic antineoplastics such as cyclophosphamide, docetaxel, paclitaxel and gemcitabine. Previous research of a retrospective cohort has shown an increased risk of MRONJ in patients who underwent a tooth extraction who were taking corticosteroids, immunosuppressants, biological drugs and/or disease modifying anti-rheumatic drugs.[38]

Aside from cancer and osteoporosis, there are an increasing number of other conditions with case reports of MRONJ, such as rheumatoid arthritis (RA).[14, 39, 40] Several implicated drugs in this study, including adalimumab, cyclophosphamide, etanercept, methotrexate and rituximab, have indications for RA as well as other auto-immune conditions.. The disease process of RA is characterised by high levels of proinflammatory cytokines that leads to increased bone resorption, progressive joint destruction, osteoporosis and increased fracture risk.[29, 41] RA is a risk factor for periodontitis, which is also recognised as a risk factor for MRONJ.[7] Both RA and MRONJ possess similar inflammatory markers in their pathogenesis: gamma-delta T cells and other pro-inflammatory cytokines (including interleukin-1 and TNF-alpha); oxidative stress; pro-inflammatory cytokines. Further, RA can affect the jaw, as seen in both RA affecting the temporomandibular joint as well as being associated with periodontitis.[41] Patients with RA may also be treated with antiresorptive drugs to treat or prevent osteoporosis, both of which are established ONJ risk factors. All these factors coupled with the use of anti-resorptives, traditional agents or targeted therapies that can cause immunosuppression and affect bone turnover, compound a patient's risk for MRONJ. Further study needs to be undertaken to assess the underlying disease that may be contributing to increased MRONJ risk.

Aromatase inhibitors anastrozole, exemestane and letrozole are used in hormone-receptor positive breast cancer and docetaxel is often used for patients with prostate cancer. Due to the

effects of estrogen on bone density, these medications are associated with a profound increase in bone turnover markers, increased bone loss with subsequent high risk of skeletal fractures.[42] Subsequently, these patients are often prescribed an antiresorptive medicine to increase bone density.[42] Patients with breast and prostate cancer are often treated with multiple medications including immunosuppressants and chemotherapy agents with complex effects on the immune system and bone, not to mention the patients' ill-health, making it difficult to determine from the information provided which medication, if any, is the most likely causative agent. However, all these medications should be considered by researchers when evaluating possible association with MRONJ.

Methotrexate has had several documented case reports associated with MRONJ,[36, 43, 44] and was associated in one case in the DAEN presented here. It has been reported to inhibit bone formation and is associated with increased bone resorption by inhibiting osteoblast proliferation and affecting osteoclast density.[39] Additionally, by suppression of the bone marrow and causing immunosuppression, there are several plausible mechanisms by which methotrexate can be associated with MRONJ.[45]

Teriparatide, a human parathyroid hormone analogue, was listed in the DAEN as a suspected causative agent in two cases, with no other drugs listed. While this drug may have contributed to MRONJ, it is unlikely because its mechanism of action is anabolic and is used in patients with severe osteoporosis,[46] the latter of which may predispose to ONJ and such patients are likely to have been treated with bisphosphonates or denosumab prior to the teriparatide. Indeed, there are several published reports where teriparatide has been used to treat MRONJ.[47] This highlights the importance of a comprehensive medical and medication history including drugs used in the past, when considering the causality of adverse events.

A principle limitation of using cases from spontaneous ADR reporting is that reports are largely based on suspicion only and reflect the observations of an individual reporter and, as such, drug causality is not proven. In addition, details such as severity and duration of medication action, dosage, strength or duration of the medicine use are not provided. Where

multiple medicines are being taken it is difficult to determine the suspected causative agent(s). Additionally, due to the lack of clinical data presented in single cases of MRONJ reported with drugs such as rituximab and mycophenolate it is unclear these drugs are the only cause as it could be due to other concurrent medicines or other risk factors not listed. The objective of reporting these is for clinicians to consider these drugs as possibilities when observing cases of MRONJ. A further limitation of ADR reporting data is the aforementioned "tip-of-the-iceberg" effect in that most ADRs go unreported due to lack of time, interest, and awareness, especially if clinicians believe an adverse drug effect is already well-known. This may be the case for the greater number of cases of MRONJ associated with denosumab compared with bisphosphonates, since bisphosphonates have been used in clinical practice for much longer. As the number of reports wanes, which may be misinterpreted as improved drug safety whereas it is more likely due to lack of reporting. As it is well-established that adverse drug reactions are under-reported, these cases do not represent all cases of MRONJ in Australia. In addition, the relationship between the suspected medicine/s and outcome of MRONJ in each case report has not been confirmed in the present study, and it is possible that MRONJ was a coincidental finding. However, this is unlikely, as it is documented that this multifactorial disease often has a trigger and that medicines are usually a contributing factor. In a small number of cases, MRONJ can occur spontaneously.[48] An accepted weakness of ADR reporting is that the occasional report will be of unlikely causality. This is accepted because the purpose of ADR reporting is identification of ADR trends, so-called "signal detection", from accumulated data.[49] In order for signal detection to be meaningful, pharmacovigilance centres require a high volume of data, so they do not risk discouraging ADR reporters by subjecting individual reports to extensive critique or assessment. Trends of causality assessment are then identified as data accumulates from global ADR reports. Finally, the database also does not include past drug history, for example patients may have been on antiresorptive medicines which were ceased at the time of ONJ diagnosis so would not have been reported but would be a contributing factor.

Regardless, the results of this analysis of medications that have effects on bone turnover provide possible drugs for consideration for clinicians in the pathogenesis of MRONJ.

Further research is needed to verify some implicated drugs and their association with MRONJ, alone or as contributing factors. The literature of agents without antiresorptive properties is relatively sparse, but growing. It is important to consider all medications that directly or indirectly affect bone turnover and healing ability, and past drug history on diagnosis. Further research can be directed at comparing these reports to maxillofacial surgery databases in major Australian institutions if documented cases of MRONJ exhibit similar associated drugs. As MRONJ is a rare complication, this study also underscores the importance of reporting suspected ADR's to a regulatory agency such as the TGA.

Conclusion

The present study adds to the sparse literature of case reports of MRONJ associated with drugs without antiresorptive properties. MRONJ is a complex multifactorial disease with many dental, anatomical, systemic and medication risk factors that contribute to its aetiology. This risk assessment and identification of risk factors are imperative for informed consent. This study presents several medications that may contribute to the pathogenesis of MRONJ, highlighting the importance of considering all possible medications that have effects on bone healing. Further research and improved MRONJ reporting are needed to verify the association of some of these drugs without anti-resorptive properties with MRONJ.

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Conflict of interest

The authors report no conflict of interest.

Data availability statement:

The data used in this study was obtained from Therapeutic Goods Administration administered by the Australian Government Department of Health. The data is de-identified, publicly available and did not identify any individual, so ethics approval was not required. The data that support the findings of this study are available on request from the corresponding author.

Author contributions

LT conceived the methodology, acquired the data from TGA, complied the results, analysed and interpreted the data, drafted the manuscript and gave final approval. GM conceived the methodology, assisted with the analysis and interpretation of the results, drafted the manuscript and gave final approval. APN assisted with the analysis and interpretation of the results and gave final approval. MMc contributed to the analysis and interpretation of the data, presentation of the results, drafted the manuscript and gave final approval.

References

1. Ruggiero SL, Dodson TB, Fantasia J, Goodday R, Aghaloo T, Mehrotra B, O'Ryan F, American Association of O, Maxillofacial S. American Association of Oral and Maxillofacial Surgeons position paper on medication-related osteonecrosis of the jaw--2014 update. J Oral Maxillofac Surg 2014; 72: 1938-56.
2. Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003; 61: 1115-7.
3. Schiodt M, Reibel J, Oturai P, Kofod T. Comparison of nonexposed and exposed bisphosphonate-induced osteonecrosis of the jaws: a retrospective analysis from the Copenhagen cohort and a proposal for an updated classification system. Oral Surg Oral Med Oral Pathol Oral Radiol 2014; 117: 204-13.
4. Fedele S, Bedogni G, Scoletta M, Favia G, Colella G, Agrillo A, Bettini G, Di Fede O, Oteri G, Fusco V, Gabriele M, Ottolenghi L, Valsecchi S, Porter S, Fung PP, Saia G, Campisi G, Bedogni A. Up to a quarter of patients with osteonecrosis of the jaw associated with antiresorptive agents remain undiagnosed. Br J Oral Maxillofac Surg 2015; 53: 13-7.

5. Lombard T, Neirinckx V, Rogister B, Gilon Y, Wislet S. Medication-Related Osteonecrosis of the Jaw: New Insights into Molecular Mechanisms and Cellular Therapeutic Approaches. Stem Cells Int 2016; 2016: 8768162.
6. Mavrokokki T, Cheng A, Stein B, Goss A. Nature and frequency of bisphosphonate-associated osteonecrosis of the jaws in Australia. J Oral Maxillofac Surg 2007; 65: 415-23.
7. McGowan K, McGowan T, Ivanovski S. Risk factors for medication-related osteonecrosis of the jaws: A systematic review. Oral Diseases 2018; 24: 527-36.
8. Filleul O, Crompot E, Saussez S. Bisphosphonate-induced osteonecrosis of the jaw: a review of 2,400 patient cases. J Cancer Res Clin Oncol 2010; 136: 1117-24.
9. Dodson TB. The Frequency of Medication-related Osteonecrosis of the Jaw and its Associated Risk Factors. Oral Maxillofac Surg Clin North Am 2015; 27: 509-16.
10. McGowan K, Ware RS, Acton C, Ivanovski S, Johnson NW. Full blood counts are not predictive of the risk of medication-related osteonecrosis of the jaws: a case-control study. Oral Surg Oral Med Oral Pathol Oral Radiol 2019; 128: 373-80.
11. Enciso R, Keaton J, Saleh N, Ahmadieh A, Clark GT, Sedghizadeh PP. Assessing the utility of serum C-telopeptide cross-link of type 1 collagen as a predictor of bisphosphonate-related osteonecrosis of the jaw: A systematic review and meta-analysis. Journal of the American Dental Association (1939) 2016; 147: 551-60 e11.
12. Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, Reid IR, Ruggiero SL, Taguchi A, Tetradis S, Watts NB, Brandi ML, Peters E, Guise T, Eastell R, Cheung AM, Morin SN, Masri B, Cooper C, Morgan SL, Obermayer-Pietsch B, Langdahl BL, Al Dabagh R, Davison KS, Kendler DL, Sandor GK, Josse RG, Bhandari M, El Rabbany M, Pierroz DD, Sulimani R, Saunders DP, Brown JP, Compston J, International Task Force on Osteonecrosis of the J. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015; 30: 3-23.
13. Galis B, Zajko J, Hirjak D, Vanko L, Kupcova I, Jurkemik J, Gengelova P, Mikuskova K, Halmova K, Riznic M, Czako L. Is the prevalence of the medication-related osteonecrosis of the jaws underestimated, evaluation in oncological and non-oncological disease. Bratisl Lek Listy 2017; 118: 724-31.
14. McGowan K, Acton C, Ivanovski S, Johnson NW, Ware RS. Systemic comorbidities are associated with medication-related osteonecrosis of the jaws: Case-control study. Oral Dis 2019; 25: 1107-15.
15. Pimolbutr K, Porter S, Fedele S. Osteonecrosis of the Jaw Associated with Antiangiogenics in Antiresorptive-Naive Patient: A Comprehensive Review of the Literature. Biomed Res Int 2018; 2018: 8071579.
16. Nicolatou-Galitis O, Kouri M, Papadopoulou E, Vardas E, Galiti D, Epstein JB, Elad S, Campisi G, Tsoukalas N, Bektas-Kayhan K, Tan W, Body JJ, Migliorati C, Lalla RV, Group MBS. Osteonecrosis of the jaw related to non-antiresorptive medications: a systematic review. Support Care Cancer 2019; 27: 383-94.
17. Fusco V, Santini D, Armento G, Tonini G, Campisi G. Osteonecrosis of jaw beyond antiresorptive (bone-targeted) agents: new horizons in oncology. Expert Opin Drug Saf 2016; 15: 925-35.
18. Australian Government Department of Health TGA. Database of Adverse Event Notifications (DAEN). In.

19. Otto S, Pautke C, Van den Wyngaert T, Niepel D, Schiodt M. Medication-related osteonecrosis of the jaw: Prevention, diagnosis and management in patients with cancer and bone metastases. Cancer Treat Rev 2018; 69: 177-87.
20. Raje N, Terpos E, Willenbacher W, Shimizu K, Garcia-Sanz R, Durie B, Legiec W, Krejci M, Laribi K, Zhu L, Cheng P, Warner D, Roodman GD. Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. Lancet Oncol 2018; 19: 370-81.
21. Wickham N, Crawford A, Carney AS, Goss AN. Bisphosphonate-associated osteonecrosis of the external auditory canal. J Laryngol Otol 2013; 127 Suppl 2: S51-3.
22. Nicolatou-Galitis O, Migkou M, Psyrri A, Bamias A, Pectasides D, Economopoulos T, Raber-Durlacher JE, Dimitriadis G, Dimopoulos MA. Gingival bleeding and jaw bone necrosis in patients with metastatic renal cell carcinoma receiving sunitinib: report of 2 cases with clinical implications. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 113: 234-8.
23. Abel Mahedi Mohamed H, Nielsen CEN, Schiodt M. Medication related osteonecrosis of the jaws associated with targeted therapy as monotherapy and in combination with antiresorptives. A report of 7 cases from the Copenhagen Cohort. Oral Surg Oral Med Oral Pathol Oral Radiol 2018; 125: 157-63.
24. Committee EA. Australian Medicines Handbook. 2019.
25. Martini V BR, Mariani U. Osteonecrosis of the jaw in a patient treated with zoledronic acid and everolimus: a case report. Annali de Stomatologia 2014; Suppl.2: 56.
26. Kim DW, Jung YS, Park HS, Jung HD. Osteonecrosis of the jaw related to everolimus: a case report. Br J Oral Maxillofac Surg 2013; 51: e302-4.
27. Akkach S, Shukla L, Morgan D. Everolimus-induced osteonecrosis of the jaw in the absence of bisphosphonates: a case report. Br J Oral Maxillofac Surg 2019; 57: 688-90.
28. Franks ME, Macpherson GR, Figg WD. Thalidomide. Lancet 2004; 363: 1802-11.
29. Manara M, Sinigaglia L. Bone and TNF in rheumatoid arthritis: clinical implications. RMD Open 2015; 1: e000065.
30. Cassoni A, Romeo U, Terenzi V, Della Monaca M, Rajabtork Zadeh O, Raponi I, Fadda MT, Polimeni A, Valentini V. Adalimumab: Another Medication Related to Osteonecrosis of the Jaws? Case Rep Dent 2016; 2016: 2856926.
31. Preidl RH, Ebker T, Raithel M, Wehrhan F, Neukam FW, Stockmann P. Osteonecrosis of the jaw in a Crohn's disease patient following a course of Bisphosphonate and Adalimumab therapy: a case report. BMC Gastroenterol 2014; 14: 6.
32. Fleissig Y, Regev E, Lehman H. Sunitinib related osteonecrosis of jaw: a case report. Oral Surg Oral Med Oral Pathol Oral Radiol 2012; 113: e1-3.
33. Patel V, Sproat C, Kwok J, Tanna N. Axitinib-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol 2017; 124: e257-e60.
34. Pilanci KN, Alco G, Ordu C, Sarsenov D, Celebi F, Erdogan Z, Agacayak F, Ilgun S, Tecimer C, Demir G, Eralp Y, Okkan S, Ozmen V. Is administration of trastuzumab an independent risk factor for developing osteonecrosis of the jaw among metastatic breast cancer patients under zoledronic acid treatment? Medicine (Baltimore) 2015; 94: e671.
35. Manzie T, Vujcich N, Chan A. Osteonecrosis of the jaw in an anti-resorptive naive patient taking trastuzumab and pertuzumab: case report. Aust Dent J 2019.
36. Henien M, Carey B, Hullah E, Sproat C, Patel V. Methotrexate-associated osteonecrosis of the jaw: A report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol 2017; 124: e283-e87.

37. Greenberger S, Boscolo E, Adini I, Mulliken JB, Bischoff J. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. N Engl J Med 2010; 362: 1005-13.
38. Hayashi M, Morimoto Y, Iida T, Tanaka Y, Sugiyama S. Risk of Delayed Healing of Tooth Extraction Wounds and Osteonecrosis of the Jaw among Patients Treated with Potential Immunosuppressive Drugs: A Retrospective Cohort Study. Tohoku J Exp Med 2018; 246: 257-64.
39. Annussek T, Kleinheinz J, Thomas S, Joos U, Wermker K. Short time administration of antirheumatic drugs - methotrexate as a strong inhibitor of osteoblast's proliferation in vitro. Head Face Med 2012; 8: 26.
40. Di Fede O, Bedogni A, Giancola F, Saia G, Bettini G, Toia F, D'Alessandro N, Firenze A, Matranga D, Fedele S, Campisi G. BRONJ in patients with rheumatoid arthritis: a multicenter case series. Oral Dis 2016; 22: 543-8.
41. Conte Neto N, Bastos AS, Chierici-Marcantonio RA, Marcantonio E, Jr. Is rheumatoid arthritis a risk factor for oral bisphosphonate-induced osteonecrosis of the jaws? Med Hypotheses 2011; 77: 905-11.
42. Perez EA, Weilbaecher K. Aromatase inhibitors and bone loss. Oncology (Williston Park) 2006; 20: 1029-39; discussion 39-40, 42, 48.
43. Furukawa S, Oobu K, Moriyama M, Kawano S, Sako S, Hayashida JN, Matsubara R, Ogata KI, Kiyoshima T, Nakamura S. Oral Methotrexate-related Lymphoproliferative Disease Presenting with Severe Osteonecrosis of the Jaw: A Case Report and Literature Review. Intern Med 2018; 57: 575-81.
44. Furudate K, Satake A, Narita N, Kobayashi W. Methotrexate-Related Lymphoproliferative Disorder in Patients With Osteonecrosis of the Jaw: A 3-Case Report and Literature Review. J Oral Maxillofac Surg 2018; 76: 97-111.
45. Mathai PC, Andrade NN, Aggarwal N, Nerurkar S, Kapoor P. Low-dose methotrexate in rheumatoid arthritis: a potential risk factor for bisphosphonate-induced osteonecrosis of the jaw. Oral Maxillofac Surg 2018; 22: 235-40.
46. Lindsay R KJ, Marin F. Jin L, Stepan J. Teriparatide for osteoporosis: importance of the full course. Osteoporos Int 2016: 2395-410.
47. Kwon YE KD. Role of Teriparatide in Medication-Related Osteonecrosis of the Jaws (MRONJ). Dentistry Journal 2016; 4.
48. Khominsky A, Lim M. "Spontaneous" medication-related osteonecrosis of the jaw; two case reports and a systematic review. Aust Dent J 2018; 63: 441-54.
49. Uppsala Monitoring Centre. Global pharmacovigilance. What is a signal? URL: https://www.who-umc.org/research-scientific-development/signal-detection/what-is-a-signal/ Accessed 18 November 2020.