Systematic review of the use of pentoxifylline and tocopherol for the treatment of medication-related osteonecrosis of the jaw

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Objective. Medication-related osteonecrosis of the jaw (MRONJ) is a pathologic process resulting in progressive destruction of the jaws. There are no established guidelines for the medical management of MRONJ. Interest in pentoxifylline and tocopherol is growing because these agents have been shown to be effective in treating osteoradionecrosis of the jaw. This review evaluates the clinical usefulness of pentoxifylline and tocopherol in treating MRONJ.

Study Design. Literature databases were searched for relevant reports of pentoxifylline and tocopherol in treating MRONJ. Only English-language reports and human studies were considered.

Results. There were 3 published observational studies and 2 abstracts relevant to this topic. The combination of pentoxifylline and tocopherol is associated with subjective and objective improvements and no major adverse outcomes.

Conclusions. Pentoxifylline and tocopherol has been demonstrated to be effective for managing MRONJ nonsurgically, and, thus, this treatment modality holds promise. However, larger clinical studies are needed to optimize dose and duration. (Oral Surg Oral Med Oral Pathol Oral Radiol 2019;128:491–497)

Medication-related osteonecrosis of the jaw (MRONJ) is a debilitating condition in which patients experience progressive bone destruction in the maxilla and the mandible after exposure to bisphosphates, antiresorptive, and antiangiogenic medications. First described in 2003, prolonged bisphosphonate use is associated with painful bone exposure, either spontaneously or secondary to surgical manipulation, in the maxillofacial region that is unresponsive to surgical or medical treatments.[1] Since Marx's initial report, other oral and maxillofacial surgeons have described similar symptoms in patients receiving bisphosphonates, as well as in those prescribed biologics, including denosumab (Xgeva) and bevacizumab (Avastin).[2-4] In 2014, the American Association of Oral and Maxillofacial Surgeons (AAOMS) published a position paper recommending discontinuation of the use of the term *bisphosphonate-related osteonecrosis of the jaw (BRONJ)* and promoting the use of the term *MRONJ* to reflect the increased incidence of osteonecrosis related to medications other than bisphosphonates.[4]

Bisphosphonates, which inhibit osteoclasts resulting in decreased bone turnover, are commonly prescribed by multiple medical subspecialties (e.g., endocrinology, oncology, orthopedics) to treat a number of conditions, including osteoporosis, Paget disease, multiple myeloma, and metastasis to bone (from primary breast, prostate, and lung cancers).[5-7] It is likely that the pathogenesis of MRONJ is multifactorial, involving the synergistic effect of trauma or infection and impaired bone turnover in the setting of bisphosphonate exposure.[8] Invasive dental procedures, including dental extractions and endosseous implant placement, appear to be a sufficiently traumatic event that precedes the onset of MRONJ; however, the etiology of this condition is not well understood.[9,10] There is also anecdotal evidence to suggest that infection (e.g., periapical abscess and periodontal disease) may be a sufficient cause of necrotic bone, independent of dental extraction, in patients taking bisphosphonates and other antiresorptive drugs.[11,12] Furthermore, medical comorbidities, particularly those associated with wound healing (e.g., diabetes mellitus and tobacco history) appear to play a role in the presentation of MRONJ.[7] With a growing list of medications associated with MRONJ, multiple mechanisms have been theorized to explain the constellation of symptoms observed. Alteration of the bone remodeling process, antiangiogenesis, and persistent inflammation and/or infection of hard and soft tissues have been examined as potential causes.[2,13,14] As studies are beginning to elucidate the reality of a multimechanism pathophysiology, a wide array of treatment strategies is being used today.

Statement of Clinical Relevance

Medication-related osteonecrosis of the jaw is a potentially debilitating disease process associated with a growing list of medications. There is presently no consensus on the ideal management of this condition.

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There are currently no established guidelines regarding the clinical management of MRONJ.[4,15] Several strategies have been employed, ranging from conservative therapy with antimicrobial mouth rinses (e.g., chlorohexidine) and antibiotics to surgical resection of necrotic bone.[16,17] A number of adjunctive therapies have also been used, including low-level laser therapy, fluorescence-guided surgery, recombinant human parathyroid hormone, and hyperbaric oxygen.[18-23] One treatment strategy that has been gaining popularity is the use of pentoxifylline with tocopherol.

The combination of pentoxifylline and tocopherol has been previously used in the management of osteoradionecrosis, with significant improvement in symptomatology.[24] Pentoxifylline is a methylxanthine derivative that has been used for management of various peripheral vascular diseases; although its mechanism remains obscure, this drug is known to lower blood viscosity, promote fibrinolysis, and enhance erythrocyte distensibility. Additionally, pentoxifylline exerts anti-inflammatory and antioxidant effects, principally by decreasing neutrophil activation as well as lowering plasma levels of tumor necrosis factor α and interleukin-1 (IL-1) and IL-6.[25-27] Tocopherol is a potent oxygen radical scavenger that minimizes damage to cell membranes, reduces inflammation, and inhibits procollagen gene expression.[28] The combination of pentoxifylline and tocopherol is thought to play a role in promoting wound healing and reducing scar formation.[15]

Because of the growing interest in the application of this therapeutic strategy, we aimed to complete a systematic literature review to evaluate the evidence regarding the effectiveness of pentoxifylline and tocopherol in treating MRONJ.

MATERIALS AND METHODS

To increase the transparency and reproducibility of this review, we reviewed and utilized the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) reporting guidelines.[29] A librarian conducted the comprehensive literature review search by utilizing a combination of subject headings and keywords in PubMed (NLM) and translated the search for EMBASE (Elsevier), Scopus (Elsevier), Cochrane Central Register of Controlled Trials (CENTRAL) and the Dentistry and Oral Sciences Source-DOSS (EBSCOHost) databases. A clinical trials registry (ClinicalTrials.gov) search and an additional search of the gray literature were also conducted. All completed search strategies are provided in Appendix A. The search was completed on February 1, 2019, and date restrictions were not introduced. Databases were searched from the point of their inception. Duplicates were removed by using Endnote X.7. Studies were screened by title and abstract by 2 independent reviewers, and a third reviewer was consulted to resolve any disagreement. The process was then repeated, and articles were screened by full text. Screening was still independent and blinded, with a third reviewer involved when needed. Articles were selected on the basis of predefined inclusion and exclusion criteria. Studies were included if they met the following criterion: use of pentoxifylline and tocopherol for the treatment of MRONJ. Studies were excluded in the presence of the following factors: non−English-language articles, review articles, and nonhuman studies (both animal and in vitro studies).

RESULTS

The article-selection workflow is summarized in Figure 1. Initial survey of the available literature yielded 7094 unique articles. Of these, 1085 articles were relevant to MRONJ/BRONJ, and 59 articles examined the use of pentoxifylline and/or tocopherol. Of the 59 articles, 6 articles specifically examined the therapeutic value of pentoxifylline and tocopherol in treating MRONJ. Three of these articles published patient data, 2 citations were published poster abstracts, 1 citation was a task force document.

The 3 articles (2 case series, 1 case report) included 14 patients[30-32] (9 females, 5 males; average age 66.79 years). Zoledronic acid was used by 10 of the patients, denosumab was used by 3 patients, alendronate was used by 3 patients, and ibandronate was used by 1 patient. The most common presenting complaint was pain, followed by infection (acute or recurring). Twelve patients presented with exposed bone, 1 patient had bony spicules but no large bony exposure, and 1 patient presented with no exposed bone. All 3 studies prescribed 400 mg pentoxifylline 2 times a day. The dosing of tocopherol was variable (500 mg twice a day vs 400 mg twice a day vs 400 IU twice a day). Additionally, all patients were instructed to rinse with 0.12% chlorohexidine twice daily. Patients with signs of acute infection were prescribed antibiotics, as needed. The average follow-up period was 13 months. All 14 patients were reported to be free from pain, erythema, swelling, and purulence at the end of their therapy. There were no reports of adverse events related to the pentoxifylline and tocopherol regimen. Table I summarizes the pre- and post-therapy findings from the 14 studied cases.

In addition to the full-text articles, there were 2 published presentation abstracts on this topic by Cheng et al.[33] and Ribeiro da Silva et al.[34] Cheng et al. presented a case series of 44 patients that were referred to the department of oral and maxillofacial surgery for oral/dental assessment before the use of bisphosphonates to treat primary or metastatic cancer, 7 of whom

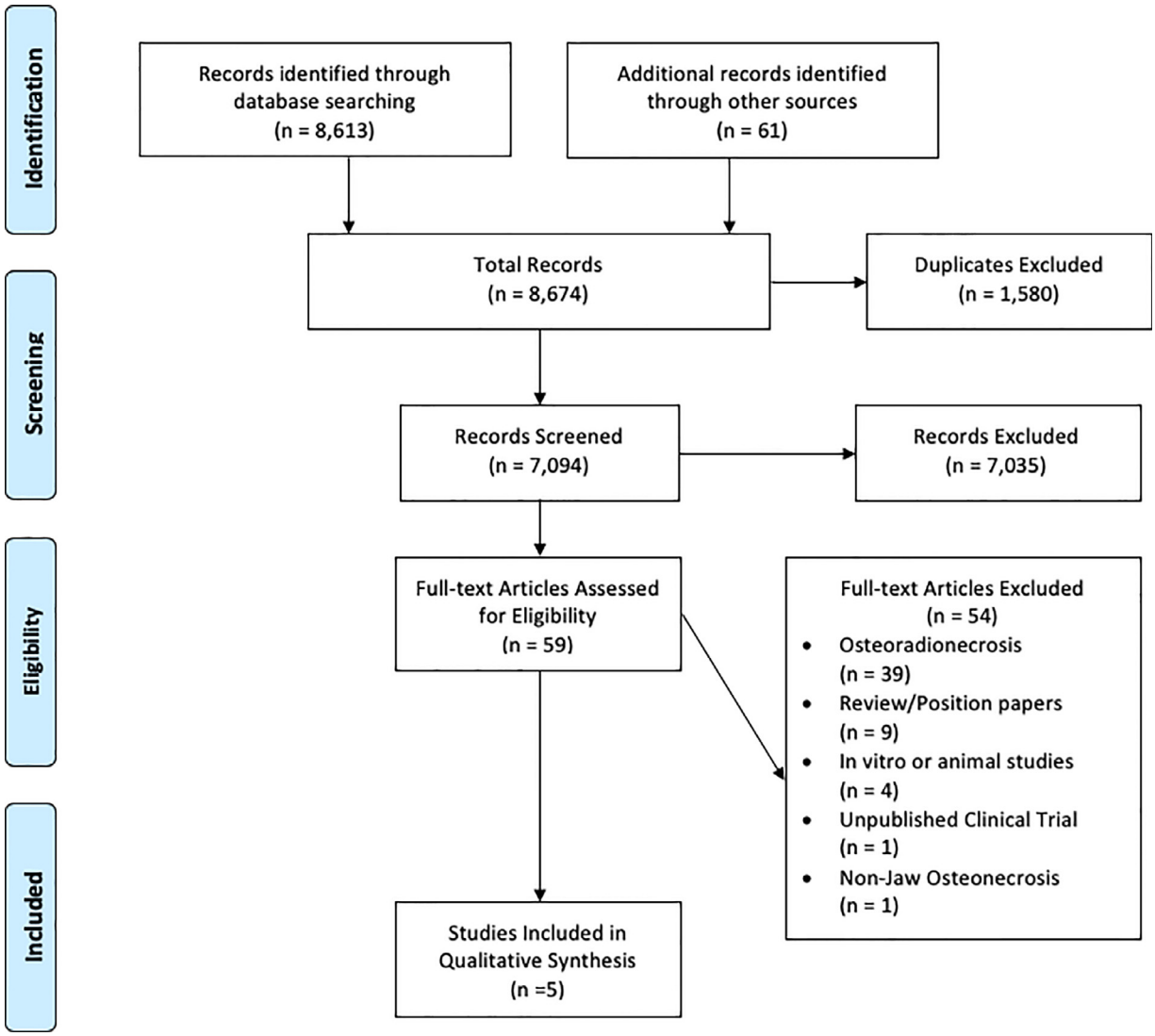

Fig. 1. Flow diagram for study selection.

had established BRONJ. These 7 patients were treated with quadruple therapy: calcium, vitamin D, pentoxifylline, and tetracycline.[33] Three of the 7 (42.85%) experienced resolution of orocutaneous fistula and 2 of the 7 (28.57%) required mandibular sequestrectomy. Ribeiro da Silva et al. presented a 120-patient case series that combined the use of pentoxifylline and tocopherol with surgical therapy.[34] In this case series, 108 patients (90%) needed surgical treatment, and an additional 12 patients (10%) who received the combination of pentoxifylline and tocopherol experienced significant improvement in signs and symptoms.

To date, no data have been published by the clinical trial "Pentoxifylline and Tocopherol (PENTO) in the Treatment of Medication-related Osteonecrosis of the Jaw (MRONJ)." A team led by Dr. Jasjit Dillon at the University of Washington is presently recruiting patients as part of a phase III clinical trial, with additional recruiting sites at the University of Alabama at Birmingham, the University of Michigan, and the New York Center for Orthognathic and Maxillofacial Surgery.[35]

DISCUSSION

Surgical removal of exposed necrotic bone is the mainstay of treatment for late-stage MRONJ; however, there are currently no well-defined treatment guidelines for the medical management of MRONJ.[4] Several nonoperative options explored before include plasma-rich protein, recombinant human parathyroid hormone, low-level laser therapy, fluorescence-guided surgery, and hyperbaric oxygen.[15] There is evidence to suggest that pentoxifylline with tocopherol is a relatively inexpensive, easy-to-use, safe, and effective treatment for osteoradionecrosis of the jaw.[24] Inspired by the growing interest in nonsurgical/medical management of MRONJ,

Table I. Summary of MRONJ patient outcomes following administration of pentoxifylline and vitamin E

Patient	*Demographic characteristics (age/gender/ stage)*	*Predisposing medication*	*Clinical presentation before pentoxifylline and vitamin E*	*Pentoxifylline and vitamin E protocol*	*Length of follow-up*	*Clinical presentation at final follow-up*	*Systemic antibiotics*
1	58/F/3	Zoledronate	Pain, purulence, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 mg BID) Peridex	3 months	No pain, erythema, or purulence 16% decrease in area of exposed bone	Yes
2	89/F/3	Pamidronate Zoledronate	Pain, purulence, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 mg BID) Peridex	19 months	No pain, erythema, or purulence 92% decrease in area of exposed bone	Yes
3	64/F/3	Aredia	Pain, purulence, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 mg BID) Peridex	12 months	No pain, erythema, or purulence 83% decrease in area of exposed bone	Yes
4	85/F/3	Alendronate	Pain, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 mg BID) Peridex	12 months	No pain, erythema, or purulence 94% decrease in area of exposed bone	No
5	81/F/3	Alendronate Ibandronate	Rough/irregular bone at extraction site	Pentoxifylline (400 mg BID) Vitamin E (400 mg BID) Peridex	10 months	No pain, erythema, or purulence 100% decrease in area of exposed bone	No
6	77/M/3	Zoledronate	Rough/irregular bone at extraction site	Pentoxifylline (400 mg BID) Vitamin E (400 mg BID) Peridex	9 months	No pain, erythema, or purulence 57% decrease in area of exposed bone	No
7	58/M/3	Alendronate Zoledronate	Persistent pain, recurrent infection, lip paresthesia, bony spicule expulsion	Pentoxifylline (400 mg BID) Vitamin E (500 mg BID) Peridex	12 months	Resolved pain and paresthesia No more bony spicules CT demonstrating bony recovery	Yes
8	63/M/3	Sunitinib Zoledronate	Pain, purulence, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	48 months	No pain, discharge, or bone exposure	Yes
9	66/M/3	Alendronate Zoledronate	Pain, purulence, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	13 months	No pain or discharge, bone exposure unchanged	Yes
10	54/M/3	Zoledronate	Pain, purulence, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	22 months	No pain, discharge, or bone exposure	Yes
11	62/F/2	Denosumab Zoledronate	Pain, discharge, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	3 months	No pain or discharge, bone exposure reduced in size	Yes

(*continued*)

Table I. *(Continued)*

Patient	*Demographic characteristics (age/gender/ stage)*	*Predisposing medication*	*Clinical presentation before pentoxifylline and vitamin E*	*Pentoxifylline and vitamin E protocol*	*Length of follow-up*	*Clinical presentation at final follow-up*	*Systemic antibiotics*
12	57/F/2	Denosumab	Pain, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	5 months	No pain, bone exposure reduced in size	Yes
13	68/F/2	Zoledronate	Pain, exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	3 months	No pain, bone exposure reduced in size	Yes
14	53/F/0	Zoledronate	Pain, swelling, no exposed bone	Pentoxifylline (400 mg BID) Vitamin E (400 IU BID) Peridex	24 months	No pain or swelling	Yes

*Patient numbers 1−6 (Epstein et al.), Patient number 7 (Margremanne et al.), Patient numbers 8−14 (Owosho et al.).[30-32]
BID, twice daily; *F,* female; *IU,* international unit; *M,* male; *MRONJ,* medication-related osteonecrosis of the jaw.

our review summarizes the use of pentoxifylline with tocopherol to effectively manage osteoradionecrosis.

Epstein et al. published the first case series utilizing pentoxifylline and tocopherol to manage MRONJ in 6 patients.[32] All 6 patients presented with stage 3 MRONJ after 74.67 months of bisphosphonate therapy. The average area of bony exposure was 93.5 mm^2. Patients were prescribed twice-daily 400 mg of pentoxifylline and tocopherol and 0.12% chlorohexidine. There was no report of systemic antibiotic therapy. The average follow-up time was 10 months (minimum 3 months, maximum 12 months). All 6 patients showed improvement with pentoxifylline and tocopherol (mean % decrease: 74%) with 1 patient showing 100% resolution. One patient required removal of bony sequestrum. At the conclusion of follow-up, in addition to reduced area of exposed bone, all patients were without pain, erythema, or purulence, and no adverse events were identified.

Magremanne et al. published a follow-up case report on a 58-year-old male patient who had stage 3 MRONJ and presented to their clinic complaining of recurrent infection, pain, paresthesia of the left mandible, and multiple bony spicules from an extraction site.[30] After his last infusion of zolendronic acid, he underwent a dental extraction, which resulted in persistent pain and repeated infections at the extraction site in the following 2 weeks, and the patient developed paresthesia of the lower lip after 1 month. After 9 months of multiple courses of analgesics, antibiotics (clindamycin and doxycycline), and multiple curettages of the extraction site, the patient was referred to an oral and maxillofacial surgery clinic, where he received twice-daily 400 mg pentoxifylline and 500 mg tocopherol as well as four-times-daily chlorohexidine rinse. The patient reported near-immediate alleviation of pain and paresthesia. At the 1-year follow-up, the patient required 1 course of doxycycline (100 mg twice daily for 3 weeks). No surgical treatment was necessary. After a year of medical management, pain and paresthesia resolved, and computed tomography (CT) showed satisfactory bone recovery. Following termination of pentoxifylline and tocopherol, there was no recurrence of infection or bone exposure, and no adverse events were identified.

Owosho et al. published the largest case report, to date, on this subject.[31] His group treated 7 patients (3 patients with stage 3 MRONJ, 3 patients with stage 2 MRONJ, and 1 patient with stage 0 MRONJ), who had received an average number of 41.86 bisphosphonate doses. All patients complained of pain at the time of initial presentation. Additionally, 4 patients had radiolucent defects identified on their orthopantomograms. Patients were prescribed twice-daily 400 mg pentoxifylline and 400 IU tocopherol, as well as 0.12% chlorhexidine. When indicated, patients were prescribed amoxicillin/augmentin or clindamycin. Bony sequestrum was removed in 2 patients, 2 patients experienced complete resolution of exposed bone, 2 patients experienced partial resolution of exposed bone, and 1 patient experienced no change in exposed bone. All patients, at termination of therapy, were pain free. In patients with pretreatment radiographic defects, follow-up radiographs demonstrated filling of the bony defect, and no adverse events were identified.

Previous studies have investigated alternative nonsurgical treatment modalities, with mixed success in the management of MRONJ.[6,15] In a randomized clinical trial, hyperbaric oxygen therapy as an adjunct to

conventional therapy has shown to decrease the time to improvement of symptoms (67.9 weeks vs 39.7 weeks) and is associated with a higher rate of clinical improvement (68% vs 38%) compared with surgery and antibiotics alone; however, complete gingival recovery was achieved in only 52% of patients treated with hyperbaric oxygen therapy and 33% in patients treated with conventional therapy alone.[15,36] Teriparatide, a recombinant parathyroid hormone, has shown some promise; a retrospective study demonstrated that 100% of patients who received 20 μg of teriparatide and supplemental calcium and vitamin D daily for 6 months experienced improvement in their MRONJ symptomatology compared with 60% of patients who only received supplemental calcium and vitamin D.[37] Success in treating MRONJ with teriparatide, however, seems to be dependent on achieving optimal serum vitamin D levels as well as adequate immune status.[37,38] Low-level laser therapy is another nonsurgical treatment modality that is gaining interest; a meta-analysis of 322 patients found complete healing in 145 patients (45.3%), partial healing in 18 (5.6%), and no healing in 37 (11.5%). Notably 5 patients (91.6%) had progressive lesions in spite of therapy.[6]

CONCLUSIONS

There is presently no consensus on the medical management of MRONJ. Published observational studies have demonstrated that pentoxifylline and tocopherol are potentially useful in the nonsurgical management of MRONJ; however, these studies were insufficiently powered, limiting our ability to make definitive recommendations. There is promise that this regimen can produce similar levels of both hard and soft tissue healing with minimal side effects, cost, and financial and/or time burden compared with other nonsurgical treatment modalities. More studies are needed to determine the optimal dosing and duration.

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APPENDIX A. SEARCH STRATEGIES

PubMed (NLM)

((((((((((((((((((((((((((Medication-related-osteonecrosis[tiab] AND jaw*[tiab]) OR MRONJ[tiab] OR BRONJ[tiab] OR (Bisphosphonate-related-osteonecrosis[tiab] AND jaw*[tiab]) OR (Bisphosphonate-associated-osteonecrosis[tiab] AND jaw*[tiab]) OR "Osteonecrosis"[MESH] OR "Osteoradionecrosis" [MESH] OR Osteoradionecros*[tiab] OR Osteonecros*[tiab] OR "Bisphosphonate-Associated Osteonecrosis of the Jaw"[MESH])))) AND (Alendronate*[tiab] OR "Alendronate"[Mesh] OR "Phosphorous Acids"[Mesh] OR Denosumab[tiab] OR "Denosumab"[Mesh] OR "RANK Ligand"[Mesh] OR "Bone Density Conservation Agents" [Pharmacological Action] OR Ibandronate* [tiab] OR "Ibandronic Acid"[Mesh] OR "Diphosphonates"[Mesh] OR Neridronate*[tiab] OR neridronic-acid* [tiab] OR Pamidronate*[tiab] OR "Pamidronate"[Mesh] OR Risedronate*[tiab] OR "Risedronic Acid"[Mesh] OR Sirolimus*[tiab] OR "Sirolimus"[Mesh] OR "Polyenes" [Mesh] OR Sorafenib[tiab] OR "Sorafenib"[Mesh] OR "Pentoxifylline"[MESH] OR "Radiation-Protective Agents" [Pharmacological Action] OR Vitamin-e[tiab] OR Tocopherol*[tiab] OR "Vitamin E"[MESH] OR "Tocopherols"[MESH] OR "Tocotrienols"[MESH] OR "alpha-tocopherol"[MESH] OR "Antineoplastic Agents" [MESH] OR Antineoplastic*[tiab] OR "antineoplastic agents"[Pharmacological Action])))))) AND (treatment* [tiab])))))))))))))) AND ((humans NOT (animals NOT humans)))

Embase.com (Elsevier)

(((’medication related osteonecrosis’ NEAR/3 jaw*):ti,ab) OR ((’bisphosphonate related osteonecrosis’ NEAR/3 jaw*):ti,ab) OR ((’bisphosphonate associated osteonecrosis’ NEAR/3 jaw*):ti,ab) OR ((’medication associated osteonecrosis’ NEAR/3 jaw*):ti,ab) OR ’jaw osteonecrosis’/exp OR mronj:ti,ab OR bronj:ti,ab OR ’osteonecrosis’/exp OR ’osteoradionecrosis’/exp OR osteoradionecros*:ti,ab OR osteonecros*:ti,ab OR ’bisphosphonate-associated osteonecrosis of the jaw’/exp) AND (alendronate*:ti,ab OR ’alendronate’/exp OR ’phosphorous acids’/exp OR ’phosphorous acids’:ti,ab OR denosumab:ti,ab OR ’denosumab’/exp OR ’denosumab’:ti,ab OR ’rank ligand’/exp OR ’rank ligand’:ti,ab OR ’bone density conservation agents’:ti,ab OR ibandronate*:ti,ab OR ’ibandronic acid’/exp OR ’ibandronic acid’:ti,ab OR ’diphosphonates’/exp OR ’diphosphonates’:ti,ab OR neridronate*:ti,ab OR ’neridronic acid*’:ti,ab OR pamidronate*:ti,ab OR ’pamidronate’/exp OR ’pamidronate’:ti,ab OR risedronate*:ti,ab OR ’risedronic acid’/exp OR ’risedronic acid’:ti,ab OR sirolimus*:ti,ab OR ’sirolimus’/exp OR ’polyenes’/exp OR ’polyenes’:ti,ab OR sorafenib:ti,ab OR ’sorafenib’/exp OR ’pentoxifylline’/exp OR ’pentoxifylline’:ti,ab OR ’radiation-protective agent*’:ti,ab OR ’vitamin e’:ti,ab OR ’vitamin e’/exp OR ’tocopherols’/exp OR tocopherol*:ti,ab OR ’tocotrienols’/exp OR ’alpha-tocopherol’/exp OR ’alpha-tocopherol’:ti,ab OR ’antineoplastic agents’/exp OR ’antineoplastic agent*’:ti,ab OR antineoplastic*:ti,ab) AND treatment*:ti,ab NOT ([animals]/lim NOT [humans]/lim)

Web of Science (Clarivate Analytics)

TS=((((("medication related osteonecrosis" AND jaw*) OR (mronj OR bronj) OR ("bisphosphonate related osteonecrosis" AND jaw*) OR ("bisphosphonate associated osteonecrosis" AND jaw*) OR (osteoradionecros* OR osteonecros*) AND ((alendronate* OR "phosphorous acid*" OR denosumab* OR "rank ligand*" OR "bone density conservation agent*" OR ibandronate* OR "ibandronic acid*" OR diphosphonate* OR neridronate* OR "neridronic acid*" OR pamidronate* OR risedronate* OR "risedronic acid*" OR sirolimus* OR ’polyene* OR sorafenib* OR pentoxifylline* OR "radiation protective agent*" OR "vitamin e*" OR tocopherol* OR tocotrienol* OR "alpha tocopherol*" OR "antineoplastic agent*" OR antineoplastic*) AND treatment*:ti,ab))))

Cochrane CENTRAL (Wiley)

((((((((((((((((((((((((((Medication-related-osteonecrosis:ti,ab AND jaw*:ti,ab) OR MRONJ:ti,ab OR BRONJ:ti,ab OR (Bisphosphonate-related-osteonecrosis:ti,ab AND jaw*:ti,ab) OR (Bisphosphonate-associated-osteonecrosis:ti,ab AND jaw*:ti,ab) OR [mh Osteonecrosis] OR [mh Osteoradionecrosis] OR Osteoradionecros*:ti,ab OR Osteonecros*:ti,ab OR [mh "Bisphosphonate-Associated Osteonecrosis of the Jaw"])))) AND (Alendronate*:ti,ab OR [mh Alendronate] OR [mh "Phosphorous Acids"] OR Denosumab:ti,ab OR [mh Denosumab] OR [mh "RANK Ligand"] OR "Bone Density Conservation Agents [Pharmacological Action]" OR Ibandronate*:ti,ab OR [mh "Ibandronic Acid"] OR [mh Diphosphonates] OR Neridronate*:ti,ab OR neridronic-acid*:ti,ab OR Pamidronate*:ti,ab OR [mh Pamidronate] OR Risedronate*:ti,ab OR [mh "Risedronic Acid"] OR Sirolimus*:ti,ab OR [mh Sirolimus] OR [mh Polyenes] OR Sorafenib:ti,ab OR [mh Sorafenib] OR [mh Pentoxifylline] OR "Radiation-Protective Agents [Pharmacological Action]" OR Vitamin-e:ti,ab OR Tocopherol*:ti,ab OR [mh "Vitamin E"] OR [mh Tocopherols] OR [mh Tocotrienols] OR [mh alpha-tocopherol] OR [mh "Antineoplastic Agents"] OR Antineoplastic*:ti,ab OR "antineoplastic agents[Pharmacological Action]"))))) AND (treatment*:ti,ab)))))))))))))

AND ((humans NOT (animals NOT humans))))))))))) in Trials'

Clinicaltrials.gov
MRONJ OR Medication-related-osteonecrosis

American Association of Oral & Maxillofacial Surgeons (AAOMS)
(MRONJ OR Medication-related-osteonecrosis OR BRONJ)