# Is medication-related osteonecrosis of the jaw associated with tumor necrosis factor-α inhibition?

Stacy A. Rosenberg, BS,[a] Cesar Migliorati, DDS, MS, PhD,[b] and Georgios E. Romanos, DDS, PhD[a]

**Objective.** This article reviews the literature and evidence of the association of medication-related osteonecrosis of the jaw with tumor necrosis factor-α inhibition.

**Methods.** A systematic review was performed using electronic databases (PubMed, MEDLINE, and Embase) using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Key terms were used in the search. No restrictions were placed on publication status. Selection criteria comprised all levels of available evidence. Articles in the English language were selected up to and including July 2020. Reference lists of relevant studies were searched for additional articles. Articles were selected on the basis of inclusion and exclusion criteria. Findings from eligible studies were extracted by one reviewer and confirmed by a second. Disagreements were settled through discussion.

**Results.** The initial search of the key terms yielded 2107 articles. There were 1192 articles remaining after removal of duplicates and addition of 6 articles that were hand-selected from among reference lists of relevant studies. There were 12 eligible articles after screening. The full texts were read, and 5 articles were included on the basis of inclusion and exclusion criteria.

**Conclusions.** Further research is required to determine an association of medication-related osteonecrosis of the jaw and tumor necrosis factor-α inhibition. (Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:422−427)

There is limited literature on medication-related osteonecrosis of the jaw (MRONJ) cases associated with tumor necrosis factor (TNF)-α inhibitors; however, it has been suggested that these medications could play a role in MRONJ.[1-6] TNF-α inhibitors are outlined in Table I. The TNF-α inhibitors infliximab and golimumab are administered intravenously, and etanercept, adalimumab, and certolizumab pegol are administered subcutaneously.[7] These medications are indicated to treat immune-mediated inflammatory diseases, which include ankylosing spondylitis, Crohn disease, rheumatoid arthritis, ulcerative colitis, uveitis, and inflammatory bowel disease.[7] The focus of this review is on determining if MRONJ is associated with TNF-α inhibition.

## METHODS

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Figure 1). Electronic databases (PubMed, MEDLINE, and Embase) were searched. The following key terms were used in the search: TNF-α inhibitors, αMRONJ, jaw osteonecrosisα, ARONJ. Restrictions were not put on publication status. Selection criteria comprised all levels of evidence available. Articles in the English language were selected up to and including July 2020. Additional articles were found through the reference lists of relevant studies. Duplicate articles were removed. In the screening process, titles and abstracts that did not include adverse oral effects, such as infection, MRONJ, and osteomyelitis, associated with TNF-α inhibition therapy were excluded. Full-text articles were then assessed, and studies with radiation to the head and neck or antiresorptive or antiangiogenic therapy were excluded. Cases that did not have a diagnosis of MRONJ were excluded. Inclusion criteria required TNF-α inhibitor therapy and development of MRONJ. One reviewer extracted findings from eligible studies that were confirmed by a second reviewer. Disagreements were settled through discussion. We extracted into a summary table (Table II) information on TNF-α inhibitor(s); risk factor(s); clinical, radiographic, and histologic findings; and management. All of the articles included patients who had received TNF-α inhibitor(s) and who developed MRONJ.

## RESULTS

The initial search of the key terms yielded 2107 articles. There were 1192 articles remaining after removal of duplicates and addition of 6 articles that were hand-selected from among the reference lists of relevant studies. There were 12 eligible articles after screening. The full texts were read, and 5 articles were included on the basis of inclusion and exclusion criteria. Three full-text articles were excluded for reasons that included cases that did not specify a diagnosis of

## Statement of Clinical Relevance

Physicians very often prescribe tumor necrosis factor (TNF)-α inhibitors. The present article is a review of the current literature for the use of TNF-α inhibitors and associated complications such as osteonecrosis of the jaw.

[a]Department of Periodontology, School of Dental Medicine, Stony Brook University, Stony Brook, NY, USA.
[b]College of Dentistry, University of Florida, Gainesville, FL, USA.
Received for publication Aug 8, 2020; returned for revision Dec 5, 2020; accepted for publication Dec 10, 2020.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2020.12.001

**Table I.** Tumor necrosis factor-$\alpha$ inhibitors

| *Generic name* | *Trade name* |
|---|---|
| infliximab | Remicade |
| Etanercept | Enbrel |
| Adalimumab | Humira |
| Certolizumab pegol | Cimzia |
| Golimumab | Simponi |

MRONJ. Four full-text articles were excluded for reasons that included cases with a history of bisphosphonates, denosumab, or both. The 5 articles that were included consisted of case reports because research studies on this direct topic were not found in the current literature.

An overview of case reports investigating patients who developed MRONJ while receiving TNF-$\alpha$ inhibition therapy is shown in Table II.[2-6] Risk factors included dental extractions or implant placement. The most commonly reported TNF-$\alpha$ inhibitors leading to MRONJ were infliximab and adalimumab. These case reports examined patients who developed MRONJ with a history of TNF-$\alpha$ inhibition therapy without antiresorptive, antiangiogenic, or radiation therapy. Another systematic review of the association of osteonecrosis and osteomyelitis of the jaw with TNF-$\alpha$ inhibitor therapy noted that the current case reports have limitations; however, the research on pathophysiologic mechanisms and evidence suggest an association of MRONJ and TNF-$\alpha$ inhibition.[8]

## DISCUSSION

The biological mechanisms of medications associated with the development of MRONJ are of importance to understanding the disease pathobiology.[9] Based on what is known today, the mechanisms involved in the formation of MRONJ are multifactorial, depending on the presence of dental disease, the type and potency of medications, the exposure time, the mechanisms involved in bone remodeling, and genetic polymorphisms, among other factors. The mechanisms of TNF-$\alpha$ may provide supporting evidence for the association between MRONJ and TNF-$\alpha$ inhibition; however, there is a requirement for more research. A research study investigated the role of TNF-$\alpha$ on osteocytes,

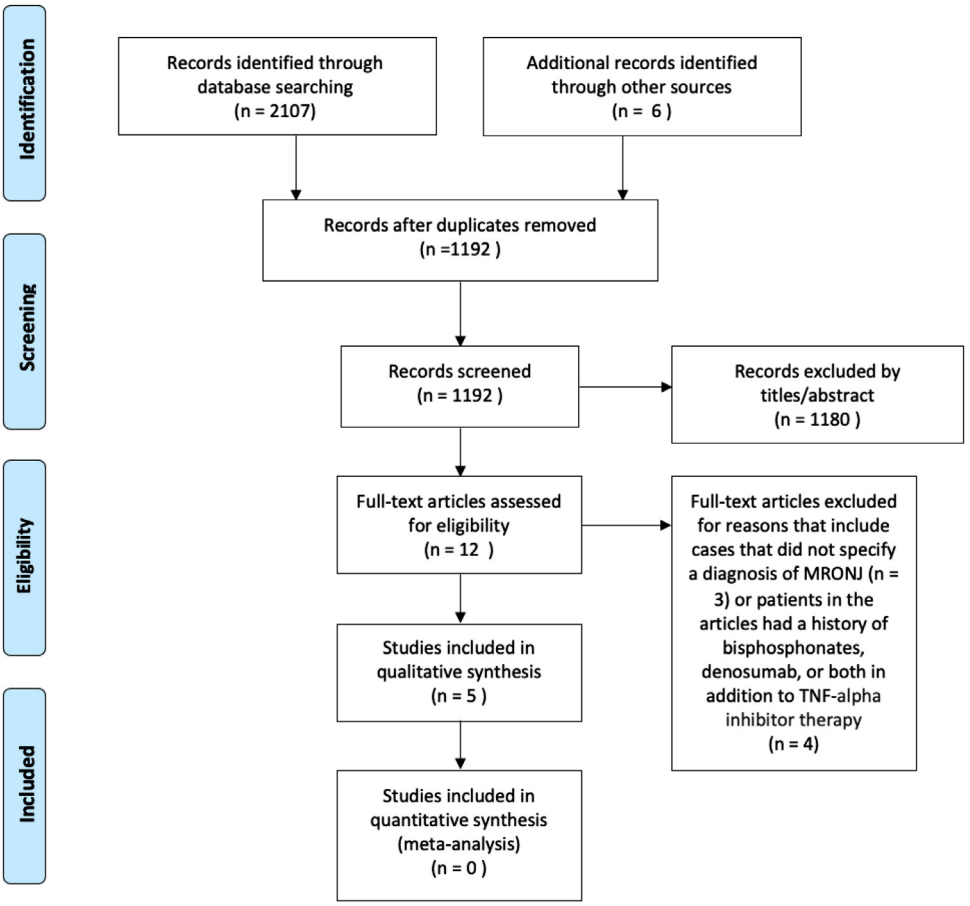


Fig. 1. Analysis of the literature based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. MRONJ, medication-related osteonecrosis of the jaw.

**Table II.** Case reports; drugs; clinical, radiographic, and histopathologic findings; and management

| *Author & year of publication* | *Number of cases* | *Drug* | *Clinical findings* | *Radiographic findings* | *Histopathologic findings* | *Management & results* |
|---|---|---|---|---|---|---|
| Cassoni et al. (2016)[2] | 1 | Adalimumab | Postoperative infection, pain, loosening teeth, alveolar bone loss, necrotic bone after placement of 4 titanium fixtures. Stage 0 MRONJ. | Osteosclerosis, osteolysis, subperiosteal bone deposition, persistence of extraction socket and sequestrum. | NA | Curettage with local antibiotics (Rifocin) for about 2-3 months, systemic antibiotic therapy (amoxicillin + clavulanic acid 1 g twice daily), systemic therapy with paracetamol and ketorolac. Healing occurred, and recurrence was not stated. |
| Favia et al. (2017)[3] | 1 | Infliximab | Intra- and extraoral 3-cm necrotic bone exposure of the anterior mandible with symptoms of submandibular swelling, pus discharge, and pain after dental extractions. Stage 3 MRONJ. | Poorly defined radiolucency in the region of bone exposure and osteolysis. | Osteonecrosis with inflammatory cell infiltration and basophilic bacterial colonies, empty Haversian canals without residual osteocytes/osteoblasts, and decreased Haversian blood vessels. | Antibiotic cycles, surgical treatment with wide bone resection and debridement of necrotic tissues. Completely healed without signs of recurrence. |
| Aghaloo & Tetradis (2017)[4] | 1 | Etanercept | Poor wound healing and bone spicules extruding from extraction site. Mildly erythematous gingiva and exposed bone on buccal aspect. Stage 2 MRONJ. | Irregular trabeculation of the alveolar ridge and extraction socket in the area of the tooth. | NA | Chlorhexidine rinses, antibiotic therapy, and debridement of bony sequestrum. Complete resolution occurred. Recurrence was not stated. |
| Cillo & Barbosa (2019)[5] | 1 | Adalimumab | Dental implant surgical site infection of 5 recently placed dental implants in the mandible with spontaneous gross purulent drainage, edema, fluctuant swelling, pain, submental and submandibular space infections, and loosening implants. | Soft tissue CT scan showed a $2.0 \times 2.0 \times 1.8$−cm fluid collection subjacent and posterior to the mandibular symphysis with extension of a submental abscess into the bilateral submandibular spaces without definitive evidence of osteomyelitis. | NA | Intravenous antibiotics, surgical and medical management, extraoral incision and drainage in the mandibular submental region, manual debridement of submental and submandibular fascial spaces after dental implant removal, discontinuation of adalimumab. Completely healed without signs of recurrence when patient began receiving adalimumab again. |

(*continued on next page*)

**Table II.** Continued

| *Author & year of publication* | *Number of cases* | *Drug* | *Clinical findings* | *Radiographic findings* | *Histopathologic findings* | *Management & results* |
|---|---|---|---|---|---|---|
| Brijs et al. (2020)[6] | 3 | Case 1: infliximab, adalimumab<br>Case 2: infliximab<br>Case 3: infliximab, adalimumab | Case 1: oroantral communication, stage 3 MRONJ.<br>Case 2: pain, stage 1 MRONJ.<br>Case 3: pain, hypesthesia of the inferior alveolar nerve, abscess, stage 2 MRONJ. | NA | NA | Case 1: Debridement and sequestrectomy. Healing occurred with recurrence 4 years later.<br>Case 2: Sequestrectomy. Healing occurred. Recurrence was not stated.<br>Case 3: Abscess incision and sequestrectomy. Healing occurred. Recurrence was not stated. |

CT, computed tomography; MRONJ, medication-related osteonecrosis of the jaw; NA, not applicable

which make up the majority of the bone cell population.[10] These researchers discussed the important function of osteocytes in bone resorption mediated by TNF-$\alpha$.[10] The study identified that TNF-$\alpha$ stimulates the nuclear factor (NF)-$\kappa$B pathway in osteocytes and directly affects osteocyte receptor activator of NF-$\kappa$B ligand (RANKL) expression both in vitro and in vivo.[10] Another study demonstrated the inhibitory effects on TNF-$\alpha$–induced osteoclastogenesis and bone resorption both in vitro and in vivo.[11] The research group identified that TNF-$\alpha$ has a fundamental role in osteoclastogenesis.[11] They challenged this by demonstrating prevention of osteoclastogenesis by TNF-$\alpha$ inhibition in the absence of RANKL, which provides evidence of the important role that TNF-$\alpha$ has in bone resorption.[11] Other studies have also shown evidence that TNF-$\alpha$ inhibition decreases bone turnover, which further suggests its association with MRONJ.[6,12-16] Additionally, it has been seen through other research studies that TNF-$\alpha$ can directly and indirectly promote osteoclastogenesis and thus can promote bone remodeling (Figure 2). This evidence may aid in our understanding of the underlying mechanisms that may have led to similar radiographic findings of TNF-$\alpha$ inhibitor–induced MRONJ to antiresorptive-induced MRONJ. The current knowledge of TNF-$\alpha$ inhibition and its effect on bone resorption may parallel the effects of antiresorptive medications and therefore may cause a similar disease process that led to comparable clinical, radiographic, and histologic findings in the current case reports. The degree to which TNF-$\alpha$ inhibitors impact bone turnover is not clear. More research on the underlying mechanisms is required to further identify how exactly MRONJ is attributed to TNF-$\alpha$ inhibition and to what severity and extent. More research is also required to determine the risk of MRONJ depending on the duration and dosage of TNF-$\alpha$ inhibitor therapy. For the interested reader, more articles on this topic can be found in the reference list.[8,10-24] TNF-$\alpha$ inhibitors can also cause reduced immune function; thus, development of MRONJ can be attributed to ongoing infections.[1-3,9,24] Compromised mucosal healing after treatment could be due to the ability of TNF-$\alpha$ inhibitors to impair wound healing that includes mucosal and bone repair of the jaw after necrosis.[1] However, another study noted that clinical signs of infection, purulent drainage, exposed bone, erythema, and fistulae may not represent the actual degree of the bone disease.[25] It is difficult to determine to what extent MRONJ from TNF-$\alpha$ inhibition results from decreased bone remodeling, infection, or a combination of both.[2] The findings discussed in the current case reports suggest an association of TNF-$\alpha$ inhibitor therapy and MRONJ. To circumvent altered clinical findings, it is also important to consider patients who

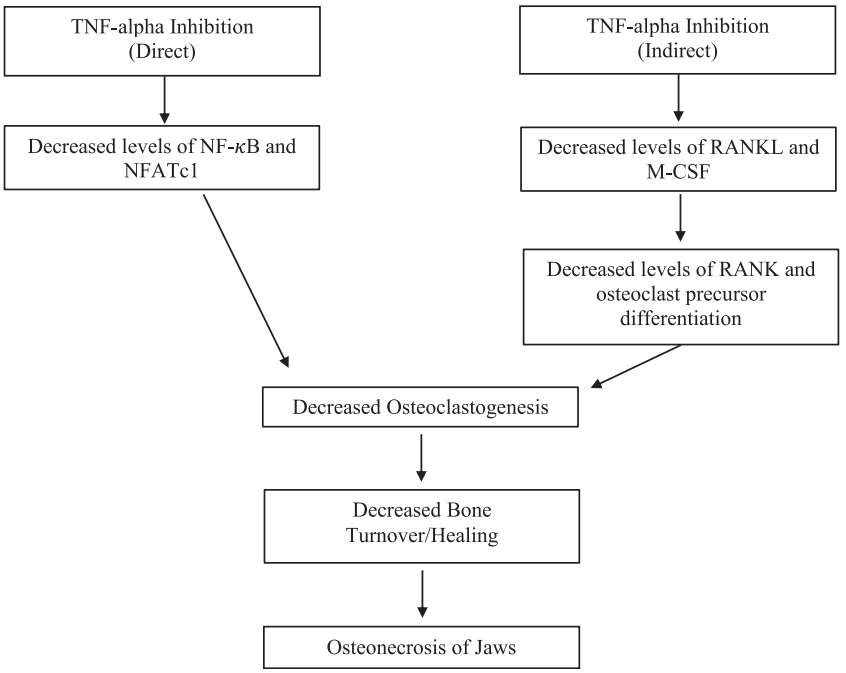


Fig. 2. Tumor necrosis factor (TNF)-$\alpha$ may activate similar signaling pathways, in terms of osteoclastogenesis directly, as the receptor activator of nuclear factor-$\kappa$B (RANK) and receptor activator of NF-$\kappa$B ligand (RANKL) system.[6,13,14] Inhibition of TNF-$\alpha$ has been identified to prevent osteoclastogenesis by decreasing expression of nuclear factor (NF)-$\kappa$B, nuclear factor of activated T cells, cytoplasmic 1 (NFATc1), through direct effects, and by decreasing levels of RANKL, RANK, and macrophage colony-stimulating factor (M-CSF) through indirect effects.[12,17,18,20]

are treated with TNF-$\alpha$ inhibitors in addition to other medications related to MRONJ. Determining an association of TNF-$\alpha$ inhibitor therapy and MRONJ requires more research, given that the current evidence summarized in Table II is based only on case reports and limited data. A statistical analysis will require more research and data.

## CONCLUSIONS

Due to the limited amount of literature and data on this topic, further research is required to determine an association of MRONJ and TNF-$\alpha$ inhibition.

## REFERENCES

1. 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.
2. Cassoni A, Romeo U, Terenzi V, Monaco MD, Zadeh OR, Raponi I, et al. Adalimumab: Another medication related to osteonecrosis of the jaws? *Case Rep Dent*. 2016;2016:2856926.
3. Favia G, Tempesta A, Limongelli L, Crincoli V, Iannone F, Lapadula G, et al. A case of osteonecrosis of the jaw in a patient with Crohn's disease treated with infliximab. *Am J Case Rep*. 2017;18:1351-1356.
4. Aghaloo TL, Tetradis S. Osteonecrosis of the jaw in the absence of antiresorptive or antiangiogenic exposure: A series of 6 cases. *J Oral Maxillofac Surg*. 2017;75:129-142.
5. Cillo JE, Barbosa N. Adalimumab-related dental implant infection. *J Oral Maxillofac Surg*. 2019;77:1165-1169.
6. Brijs K, Miclotte I, Vermeire S, Darche V, Politis C. Osteonecrosis of the jaw in patients with inflammatory bowel disease treated with tumour necrosis factor alpha inhibitors. *Int J Oral Maxillofac Surg*. 2020;49:317-324.
7. Gerriets V, Bansal P, Goyal A, Khaddour K. *Tumor necrosis factor inhibitors*. *StatPearls* [Internet]. Treasure Island, FL: StatPearls; 2020.
8. Sacco R, Shah S, Leeson R, Moraschini V, de Almeida Barros Mourão CF, Akintola O, et al. Osteonecrosis and osteomyelitis of the jaw associated with tumour necrosis factor-alpha (TNF-$\alpha$) inhibitors: A systematic review. *Br J Oral Maxillofac Surg*. 2020;58:25-33.
9. Migliorati CA, Brennan MT, Peterson DE. Medication-related osteonecrosis of the jaws. *J Natl Cancer Inst Monogr*. 2019;2019:lgz009.
10. Marahleh A, Kitaura H, Ohori F, Kishikawa A, Ogawa S, Shen WR, et al. TNF-$\alpha$ directly enhances osteocyte RANKL expression and promotes osteoclast formation. *Front Immunol*. 2019;10:2925.
11. Ohori F, Kitaura H, Ogawa S, Shen WR, Qi J, Noguchi T, et al. IL-33 inhibits TNF-$\alpha$-induced osteoclastogenesis and bone resorption. *Int J Mol Sci*. 2020;21:1130.
12. Luo G, Li F, Li X, Wang ZG, Zhang B. TNF-$\alpha$ and RANKL promote osteoclastogenesis by upregulating RANK via the NF-$\kappa$B pathway. *Mol Med Rep*. 2018;17:6605-6611.
13. Hehlgans T, Pfeffer K. The intriguing biology of the tumour necrosis factor/tumour necrosis factor receptor superfamily: Players, rules and the games. *Immunology*. 2005;115:1-20.
14. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. *Pharmacol Ther*. 2008;117:244-279.
15. Liao HJ, Tsai HF, Wu CS, Chyuan IT, Hsu PN. TRAIL inhibits RANK signaling and suppresses osteoclast activation via

inhibiting lipid raft assembly and TRAF6 recruitment. *Cell Death Dis*. 2019;10:77.
16. Ha H, Kwak HB, Le SW, Kim HH, Lee ZH. Lipid rafts are important for the association of RANK and TRAF6. *Exp Mol Med*. 2003;35:279-284.
17. Levin AD, Wildenberg ME, van den Brink GR. Mechanism of action of anti-TNF therapy in inflammatory bowel disease. *J Crohns Colitis*. 2016;10:989-997.
18. Asagiri M, Takayanagi H. The molecular understanding of osteoclast differentiation. *Bone*. 2007;40:251-264.
19. Kim JW, Landayan ME, Lee JY, Tatad JC, Kim SJ, Kim MR, et al. Role of microcracks in the pathogenesis of bisphosphonate-related osteonecrosis of the jaw. *Clin Oral Investig*. 2016;20:2251-2258.
20. Boyle WJ, Simonet WS, Lacey DL. Osteoclast differentiation and activation. *Nature*. 2003;423:337-342.
21. Kanazawa K, Kudo A. TRAF2 is essential for TNF-alpha-induced osteoclastogenesis. *J Bone Miner Res*. 2005;20:840-847.
22. Kim JH, Kim N. Regulation of NFATc1 in osteoclast differentiation. *J Bone Metab*. 2014;21:233-241.
23. Ross FP. M-CSF, c-Fms, and signaling in osteoclasts and their precursors. *Ann N Y Acad Sci*. 2006;1068:110-116.
24. Scheinfeld N. A comprehensive review and evaluation of the side effects of the tumor necrosis factor alpha blockers etanercept, infliximab and adalimumab. *J Dermatolog Treat*. 2004;15:280-294.
25. Cardoso CL, Barros CA, Curra C, Fernandes LM, Franzolin SO, Júnior JS, et al. Radiographic findings in patients with medication-related osteonecrosis of the jaw. *Int J Dent*. 2017;2017:3190301.

*Reprint requests:*

Georgios E. Romanos, DDS, PhD, Prof. Dr. med. dent.,
Department of Periodontology
School of Dental Medicine
Stony Brook University
106 Rockland Hall
Stony Brook
NY 11794-8700
georgios.romanos@stonybrook.edu