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REVIEW ARTICLE

Correlation of anti-TNF-a biological therapy with periodontal conditions and osteonecrosis in autoimmune patients: A systematic review

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KEYWORDS

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anti-TNF-a;
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Autoimmune

Abstract *Objectives:* This systematic review aims to investigate the impact of tumor necrotic factor alpha inhibitors in suppressing bone resorption in periodontitis, and its potential to cause osteonecrosis. Extensive electronic research was conducted following the PRISMA guidelines, which connected various aspects of anti-TNF-a (anti-tumor necrosis factor-a) to periodontitis and osteonecrosis patients.

Background: TNF-a inhibitors are broadly indicated in the treatment of autoimmune patients with possible joint resorption and increased inflammatory processes such as rheumatoid arthritis and inflammatory bowel disease, where they reduce bone loss and certain mediators. As rheumatoid arthritis and periodontitis share many characteristics, these medications may also be helpful in the treatment of coexisting periodontitis. However, besides medical benefits, anti-TNF-a also exhibits several adverse effects, ranging from dizziness to tuberculosis. Osteonecrosis is considered a recent adverse impact.

Methods: An extensive electronic systematic review following the PRISMA guidelines was performed for English-language papers using the following databases as sources of information: PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Library Genesis, Worldwide Science, National Rheumatoid Arthritis Society (NRAS), and other related articles. This systematic review is registered on the PROSPERO platform under registration number CRD42022341753.

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Results: Twenty articles were identified after the exclusion criteria were applied. These include systematic reviews, case reports, retrospective cohort studies, case report series, *meta*-analyses, clinical trials, randomised clinical trials, cross-sectional and longitudinal analyses, longitudinal observational studies, and prospective clinical trials. All these were included in the quantitative and qualitative analyses.

Conclusions: Anti-TNF-a drugs show promising results in treating patients with rheumatoid arthritis and periodontitis but could be considered a risk factor for osteonecrosis. Hence, patients receiving such medications should be closely monitored by the dentist and physician before, during, and after administration.

Contents

1. Introduction

1.1. Overview

In recent decades, the medical field has developed rapidly in terms of new technologies and approaches to the diagnosis and treatment of diseases (Thimbleby, 2013). With the introduction of Infliximab in 1999, biological therapy was primarily used to treat rheumatoid arthritis. These are expensive drugs to develop and produce. They mainly target cytokines (Meier et al., 2013). Different types have different effects, but the most commonly used tumor necrosis factor beta inhibitors are infliximab, adalimumab, and etanercept (Gerriets et al., 2022). We focused our research on these three drugs because they are the most commonly used and best-selling drugs worldwide (Monaco et al., 2015). As Certolizumab and golimumab were approved recently, there is still no comparative clinical trial to evaluate the efficacy of these bio-agents and their place in therapy (Garattini et al., 2016). Infliximab has been developed as a potential therapeutic agent for various chronic inflammatory diseases driven by the pro-inflammatory cell cytokine TNF-a. It is a human chimeric-type murine monoclonal antibody that neutralises the TNF-a in the body and thus reduces inflammatory processes. Adalimumab (Humira) is the first fully human single monoclonal G1 immunoglobulin (IgG1) that inhibits TNF-a. Since it is completely human, it can induce a long-term response with or without the help of other disease-modifying antirheumatic drugs (Dübel, 2007).

1.2. Immunology

Further, other types such as anti-IL (Interleukin)-1, IL-12, and IL-13 can also be used in cases where the specific inflammatory mediator is known as the cause of the disease; otherwise, anti-TNF-a drugs are used in most cases (Abreu, n.d.). These drugs can be used in the treatment of inflammatory autoimmune diseases such as rheumatoid arthritis, Crohn's disease, ankylosis spondylitis, Behcet's disease, inflammatory bowel disease, psoriasis, psoriatic arthritis, and juvenile arthritis. The differentiation between these drugs can be effortful; therefore, a

Table 1 Anti-TNF-a drugs used to treat inflammatory diseases.

Drug	Trade name	Route of administration
Infliximab	Remicade	Intravenous
Adalimumab	Humira	Subcutaneous
Etanercept	Enbrel	Subcutaneous
Golimumab	Simponi	SubcutaneousIntravenous
Certolizumab pegol	Cimzia	Subcutaneous

summary (Table 1) (Rosenberg et al., 2021) is presented with the name of the drug, the trade name, and the route of administration. Like other medications, these groups of drugs have several side effects ranging from moderate to severe that can be lethal if not treated immediately (Dübel, 2007). Moderate side effects include dizziness, rash, nerve problems, blood disorders, headaches, and allergic reactions, while more severe side effects can lead to drug-induced lupus, heart failure, infections, sepsis, and malignancies (Gerriets et al., 2022).

Till now, these drugs have not been well studied or developed, and most side effects are still not adequately explained or fully understood (Meier et al., 2013). One of the unexplained side effects of anti-TNFs-a is on oral bone and its relation to periodontal status (Muñoz-Martínez et al., n.d.). It is known that TNF-a is one of the main mediators responsible for bone resorption in periodontitis patients, as it activates and increases the maturation of osteoclasts (Heasman & Hughes, 2014). Further, new studies have revealed that it also activates matrix metalloproteinases (MMP) 8 and 9, responsible for the destruction of collagen in the periodontium (Martu et al., 2021). Theoretically, blocking TNF-a might reduce bone resorption in periodontitis (Zamri & de Vries, 2020). Further, since TNF-a is needed in bone remodeling after extractions, blocking it might have a catastrophic effect on the healing process (Ciantar & Adlam, 2007).

This systematic review aims to analyse published evidence related to the effect of TNF-a inhibitors on the bone and periodontium in autoimmune patients, and the prevalence of osteonecrosis after causal factors.

2. Materials and methods

A systematic review was conducted following the PRISMA guidelines (Fig. 1). The current systematic review is registered on the PROSPERO platform under the registration number (CRD42022341753). Extensive electronic research was performed for English language articles using the following databases as sources: PubMed, Medline, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Library Genesis, Worldwide Science, National Rheumatoid Arthritis Society (NRAS), and related articles. The keywords used in the research were mainly in three groups that are proposed to investigate the outcome following PICO (Table 4). The first group related to "anti-TNF-a and periodontitis patients", and free text terms "Infliximab", and "Adalimumab". An operator set was used to combine the results of 'anti-TNF-a drugs' and 'periodontitis in autoimmune patients'. The second group was on oral bone resorption and anti-TNF-a, jaw osteonecrosis, TNF-a inhibitors, mandibular osteomyelitis after anti-TNF-a treatment with free text terms case report, and jaw osteomyelitis. The third group primarily collected and connected information between the two subjects using "anti-TNF-a and dentistry", "Infliximab and dentistry", and "Infliximab oral complication" as keywords. Therefore, a manual selection of the studies was made that met the ensuing inclusion criteria: 1) comparative studies, *meta*-analysis reviews, case reports, observational studies, randomised control trials, systematic reviews, and multicenter cohort studies, 2) patients treated with one of the anti-TNF-a drugs; and 3) the availability and precision of the data. The exclusion criteria were studies not published in English, inaccessibility to the full published text, publications restricted from the e-resource, studies on patients treated with radiation therapy earlier and those not related to autoimmune diseases. The papers obtained belonged to the period from 1999 to 2022. There was no restriction on age, sex, and ethnicity.

3. Results

The electronic literature search retrieved 320 articles from different data sources, including primary, secondary, and tertiary. After duplicate papers were removed, a total of 280 papers were screened to exclude 188 for not meeting the eligibility criteria and PICO questions, leaving 92 articles. After applying the inclusion and exclusion criteria, 20 articles remained and were included in the qualitative and quantitative analysis in this systematic review. Exclusion criteria included conflict of interest, a weak base of results, no full text, unclear methodology, invalid findings, bias, unreliable measuring instrument, insufficient sample size, non-availability of the full text in English, animal studies, narrative reviews, articles related only to osteomyelitis and Rituximab (a monoclonal antibody but aimed at B cells), as this study is dedicated to a monoclonal antibody acting on TNF-a. The results were 5 systematic reviews, 5 case reports, 1 retrospective cohort study, 1 series of case reports, 2 *meta*-analysis reviews, 2 clinical trials, 1 randomised clinical trial, 1 cross-sectional and longitudinal analysis, 1 longitudinal observational study, and 1 prospective clinical trial. Tables 2 and 3 show the detailed results for each related article (See Table 5).

4. Discussion

4.1. Immunotherapy

From anesthetics and antibiotics to magnetic resonance imaging scanners and radiation, technological advancements have had a significant impact on healthcare and were presented as new drugs and treatments, and new equipment. Further, new social media support for healthcare will continue to revolutionise healthcare in the future (Thimbleby, 2013). A breakthrough in the pharmaceutical field was the introduction of biological therapies in the treatment of many illnesses, ranging from autoimmune diseases that could limit lifestyles to lethal diseases such as cancers and tumors (Rosman et al., 2013). Biological therapies were inspired by the concept that the human body requires some type of defensive system to combat external hazardous compounds, these substances should be present in the blood and may hence be produced from serum, and used for toxin, or infection therapy (Müller, 2006). Since

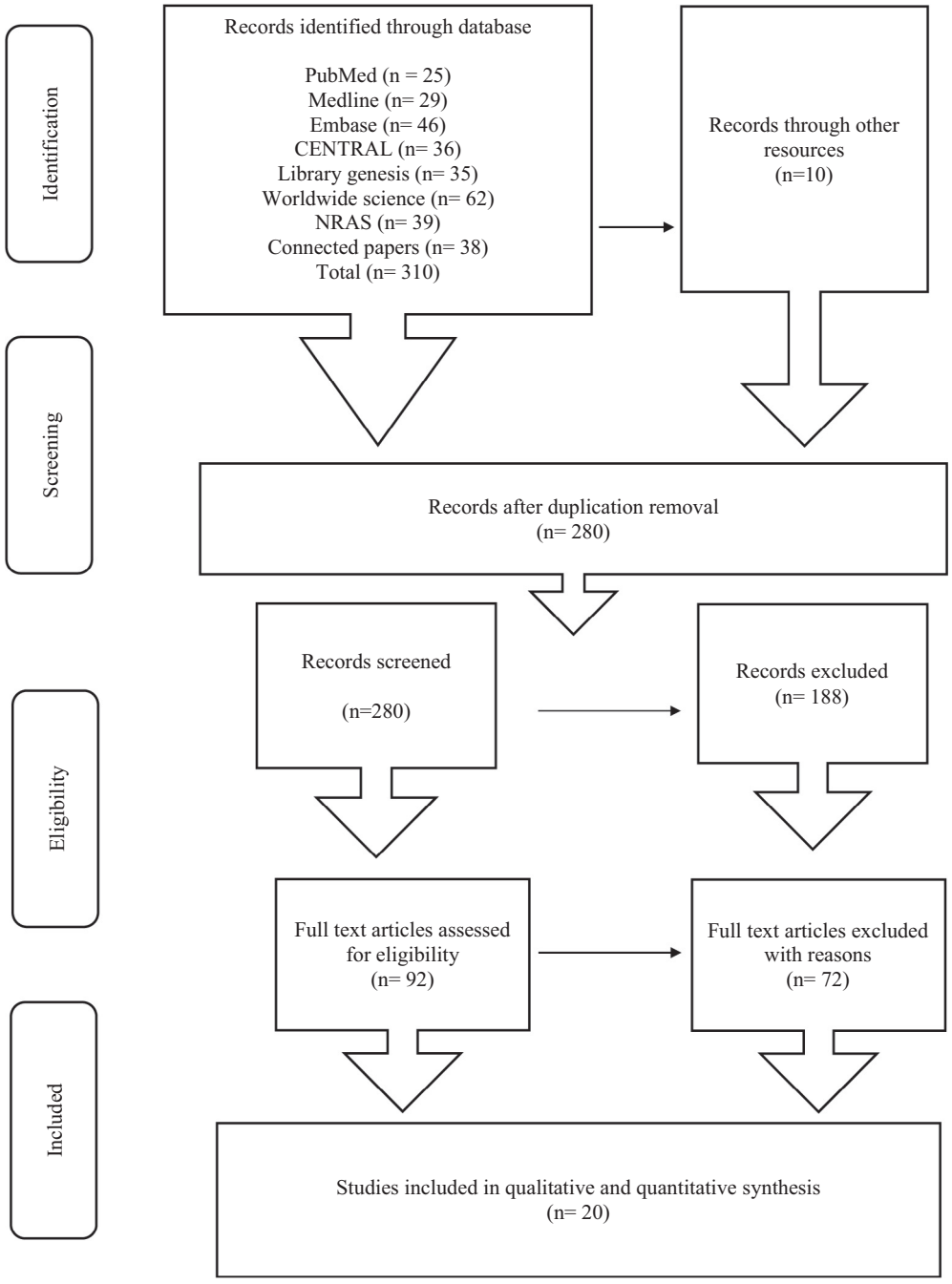

Fig. 1 Selection process following PRISMA guidelines.

then, eliminating tumor cells using antibody molecules alone, or as conjugates made up of such molecules, has piqued immunologists' interest. The first successful attempt was in 1997 when the US Food and Drug Administration (FDA) approved the use of a Rituximab antibody, which is a mouse-human monoclonal antibody used in the treatment of non-Hodgkin lymphomas (Minard-Colin et al., 2020). Since the Rituximab antibody is based on murine and human components, it has limitations for long-term use and the potential to increase the immune response (Storz, 2014). Similarly, Infliximab, a human-murine monoclonal antibody that binds to and neutralises the soluble homotrimer of TNF and its membrane-bound precursor, was developed as a possible treatment medication for a variety of chronic inflammatory diseases believed to be triggered by the pro-inflammatory cytokine TNF (Lichtenstein et al., 2015). The next in line is Etanercept, a fusion protein comprising two identical chains of human anti-TNF receptor p75 monomers linked to the human IgG1 Fc domain (Xu et al., 1999). It acts as a soluble TNF receptor and binds to TNF-alpha and TNF-beta, but is used mainly in the treatment of autoimmune diseases as an inhibitor of TNF (Pan & Gerriets, 2022).

Table 2 Results of correlation between osteonecrosis and Anti-TNF-a.

Study	Objective	Study Design	Findings	Conclusions
(Rosenberg, Migliorati and Romanos, 2021)	Review literature for a link between medication-related osteonecrosis of the jaws and inhibition of tumor necrosis factor Alpha.	Systematic review	Several articles have revealed that people using anti-TNF-a developed MROJN after being exposed to risk factors such as tooth extractions and dental implant placement.	Data and studies on pathophysiological processes point to a link between MRONJ and TNF-alpha suppression.
(Amigo-Basilio et al., 2021)	To understand the biological therapeutic drugs associated with adverse events, what dental treatments are related to the development of these events, the severity of these events, and how they are resolved.	Systematic review	In individuals treated with infliximab or with adalimumab, cases of oral infections have been recorded. After surgical manipulation, trauma, or poorly fitting prosthesis, MRONJ patients are treated with a range of biological treatments.	According to the literature, the most strongly related biological drugs in dentistry are bevacizumab, Danosumab, and sunitinib. Other biological drugs, such as Adalambu and Infleximbu, are also associated with bone osteoporosis (MRONJ), usually treated surgically.
(Sakkas and Department of Oral, Maxillofacial and Facial Plastic Surgery, Klinikum Ludwigshafen (Hospital), Ludwigshafen, Germany, 2020)	To describe a case of MRONJ in a young patient treated with infliximab, a tumor necrosis factor inhibitor used to treat immune-mediated inflammatory diseases such as Crohn's disease, ulcerative colitis, ankylosing spondylitis, rheumatoid, and psoriatic arthritis.	Case Report	TNF (adalimumab) is already linked to MRONJ in separate case reports. This patient developed osteonecrosis exacerbated by poor oral hygiene and smoking. She arrived with discomfort and swelling in her jaw, but no surgical interventions were identified. She was diagnosed with severe bone marrow osteoporosis. The patient was treated with surgical therapy, including extensive bone cutting and necrotic tissue removal.	We describe a patient who had severe jaw osteonecrosis after receiving infliximab treatment. A frequent dental examination before and during infliximab is strongly advised to prevent MRONJ from recurring or to discover lesions at an early stage.
(Favia et al., 2017)	To describe an MRONJ case in a patient using infliximab, an anti-TNF-a antibody used to treat Crohn's disease, rheumatoid arthritis, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.	Case Report	The patient was treated with infliximab and had no history of antiresorptive or antiangiogenic drug treatment. She was sent to us for stage 3 postoperative MRONJ of her anterior mandible. Several papers blamed MRONJ on denosumab, bevacizumab, rituximab, adalimumab, and sunitinib.	Although more research is needed to validate the function of infliximab in MRONJ, based on the findings of this study, we recommend that patients to be treated with infliximab should also have dental check-ups before commencing medication to avoid the emergence of MRONJ.
(Cassoni et al., 2016)	Describe the first incidence of osteonecrosis of the jaws in a woman caused by the use of Adalimumab to treat idiopathic arthritis.	Case Report	After four titanium fixings were placed in the jaw, the patient treated with Adalimumab developed osteonecrosis. DRONJ is related to the suppression of the receptor activator of the nuclear factor kappa-B ligand (RANKL), resulting in the inhibition of osteoclast activity. Anti-TNF-a medication can inhibit bone turnover through a decrease in RANKL, increasing infection, and reducing bone remodeling after necrosis.	According to the authors, biological treatment with an anti-TNF-a antibody may enhance the appearance of osteonecrosis and decrease the bone's oral healing potential.

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Table 2 (*continued*)

Study	Objective	Study Design	Findings	Conclusions
(Preidl et al., 2014)	A case report of BRONJ in a patient with oral Crohn's disease who was treated with Adalimumab.	Case Report	This patient with Crohn's disease and gastrointestinal remission on Adalimumab therapy presented with jaw osteonecrosis after suspending oral and intravenous Bisphosphonate therapy, implying that biologic therapy with an anti-TNF- antibody may promote the manifestation of osteonecrosis and compromise oral healing capacity.	Patients with Inflammatory Bowel Disease and planned treatment with biological medications such as Adalimumab, as well as a history of Bisphosphonate therapy, should be clinically evaluated by a dentist before biologicals are prescribed. Additionally, patients should be closely examined for osteonecrotic lesions of the jaw, particularly after dental treatments or within the context of periodontal disease.
(Brijs et al., 2020)	Examine the prevalence of MRONJ in a group of patients with inflammatory bowel disease (IBD) being treated with TNF-a inhibitors in a tertiary care medical institution.	Retrospective cohort study	Three patients with a clear diagnosis of MRONJ were treated with anti-TNF-a without concurrent bisphosphonate therapy. More patients were discovered who were undergoing various therapies before biological therapy.	This study is unique in that it reports the incidence of severe MRONJ in a large registry of patients with IBD using TNF-a drugs.
(Cillo and Barbosa, 2019)	To present a surgical site infection at the dental implant caused by adalimumab.	Case Report	The patient lost all his mandibular dental implants and bone, which was devastating. Apart from active adalimumab administration, there were no other medical or pharmacological causes of infection, such as active steroid usage, anti-resorptive medicines, or radiation, which might have contributed to the total early infection and dental implant failure.	Adalimumab users may have severe infections that result in implant and bone loss. When biological medications, such as adalimumab, are taken, serious postoperative oral surgical site infections can arise. Individuals using biologic drugs, such as adalimumab, who are planning to undertake elective oral or dental implant surgical procedures, should check with their prescribing physician first.
(Sacco et al., 2020)	Review all published data on jaw osteonecrosis (ONJ) and osteomyelitis (OM) in patients treated with TNF-a inhibitors who had no history of antiangiogenic or antiresorptive therapy.	Systematic review	Our data imply that some people taking these medications will develop ONJ even if they do not have the traditional risk factors for MRONJ.	Some individuals may develop ONJ/OM due to the TNF-a inhibitor drug, usually after invasive surgery.
(Aghaloo and Tetradis, 2017)	A six-case series of MRONJ related to drugs other than antiresorptive or antiangiogenic drugs was described.	Series of case reports	Diseases such as rheumatoid arthritis and the drugs used to treat them can cause poor healing and cause lesions that are clinically and radiographically comparable to ONJ. This study describes ONJ caused by etanercept, adalimumab, and rituximab.	The degree of risk of osteonecrosis in individuals using these new groups of medications is unknown, but it is important to be informed and well-monitored.

4.1.1. Mechanism of action

Etanercept exclusively binds to sTNF-a, which was considered the main enzyme responsible for inducing inflammatory responses, and not to mTNF-a, which has also been discovered recently to biologically activate similar responses. This was an advantage in the other biological drugs like Infliximab and

Table 3 Results of correlation between periodontium condition and Anti-TNF-a.

Study	Objective	Study design	Findings	Conclusions
(Zamri and de Vries, 2020)	Assess the impact of anti-TNF-a therapy on periodontal health in RA patients.	Systematic Reviews and Meta-Analyses	Anti-TNF medication improved periodontal health in trials when periodontal care was administered. However, after 30 days of use, the GI and BOP values were higher in these individuals. After 6 months, they statically significant decreased slightly for GI, PI, BOP, and CAL but, increased slightly after 9 months in GI and BOP.	According to this systematic study, anti-TNF medication is good not only for rheumatic joints but also for the gums of patients with rheumatoid arthritis.
(Mayer, Balbir-Gurman, and Machtei, 2009)	The purpose of this study was to see how antitumor necrosis factor-alpha (TNF-a) medication affected the clinical and immunological characteristics of the periodontium.	Clinical trial	People with RA had poorer periodontal and gingival conditions in our research than patients without systemic inflammatory illness. Prevention of bone resorption was achieved by inhibiting TNF-a activity. Infliximab, on the other hand, was found to increase gingival inflammation. Statistically significant between AL and + RA ($r = 0.487$; $P < 0.001$).	RA patients treated with anti-TNF-a medication exhibited reduced periodontal indices and GCF TNF-a levels. Thus, decreasing pro-inflammatory cytokines may be advantageous in the prevention of periodontal diseases.
(Kadkhoda et al., 2016)	The purpose of this study was to see how TNF-blockade affected periodontal problems in patients with active RA.	Randomized clinical trial	TNF- antagonists were shown to decrease connective tissue and bone loss in experimental periodontitis when periodontal treatment is administered. Although etanercept therapy resulted in considerable reductions in periodontal indicators of inflammation, gingival inflammation worsened following anti-TNF-medication delivery.	Anti-TNF- medication improves periodontal problems and reduces TNF- levels in individuals with RA GCF.
(Heasman and Hughes, 2014)	The purpose of this paper is to go through some of the more prevalent medicines that can impact the periodontium, whether healthy or inflamed.	Systematic review	Patients with rheumatoid arthritis who received anti-TNF-therapy in the form of regular infusions of infliximab showed that the biological therapy appeared to offer a degree of protection to patients with periodontal inflammation, with less bleeding on probing, attachment loss, and shallower probing depths when compared to patients with arthritis but no infliximab therapy.	The original study's findings revealed that the anti-TNF-drug infliximab may limit bone resorption in individuals at risk of periodontal disease, although probing depths were unaltered and, astonishingly, the intensity of gingival inflammation was enhanced.
(de Molon et al., 2019)	Examine and present an overview of the relationship between RA and PD, focusing on the parallels in immunopathological characteristics and potential pathways connecting the genesis and progression of both diseases. In addition, the currently available therapies for both RA and PD were revised.	Systematic review	TNF blockers used to treat RA patients resulted in a substantial decrease in PD biochemical markers such as IL-1 and IL-8 in the GCF of patients with developed periodontitis. Anti-TNF- therapy lowers periodontal indices and TNF- levels in the GCF of patients with autoimmune disease and periodontitis. Both illnesses benefit from their	These results showed that suppressing TNF- in the treatment of RA may also be effective in the treatment of PD. DMARD and anti-TNF medications reduced the amount of CAL in RA patients, compared to those who did not receive treatment.

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Table 3 (*continued*)

Study	Objective	Study design	Findings	Conclusions
			immunomodulatory properties.	
(Pers et al., 2008)	The likelihood that infliximab therapy for RA provides a chance to study its impact on concomitant periodontitis.	Cross-sectional and longitudinal analysis	Infliximab tended to worsen gingival inflammation, as evidenced by variations in modified gingival and papillary bleeding indices before and after therapy between participants in groups I and II with co-existing periodontitis. Statistically significant in smokers.	Our findings showed that inhibiting TNF-a activity might assist in curing periodontal disease by inhibiting bone resorption.
(Mayer et al., 2013)	Assess the impact of the treatment of autoimmune diseases (AI) and antitumor necrosis factor-a (TNF-a) on the clinical and immunological parameters of periodontal disease.	Clinical trial	Compared to the H and RA + groups, patients with AI had a higher GI. The AI patients had considerably higher BOP than the H and RA + patients. PD in the H and RA + groups was lower than in the AI group. There were no statistically significant differences between the two groups except a slight increase in GI after treatment with Infliximab.	Patients with AI disorders had higher levels of GCF TNF-a and higher periodontal indices than H controls. This tendency appears to be reversed by anti-TNF-a medication.
(Zhang et al, 2021.)	To assess the effect of various anti-rheumatic medications on periodontal health and to offer treatment advice to patients with rheumatoid arthritis (RA) and periodontitis.	Systematic review and *meta*-analysis	CsDMARDs, anti-B lymphocyte agents, anti-IL-6R agents, and anti-TNF agents were employed, demonstrating that anti-rheumatic medications were useful for improving PD, CAL, and GI in RA and periodontitis patients.	Antirheumatic drugs improved periodontal metrics in patients with RA and periodontitis. Due to their rapid onset of action, bDMARDs and tsDMARDs had an advantage over csDMARDs. Future research is needed to identify whether anti-TNF agents might increase gingival inflammation and whether anti-B lymphocyte drugs should be used first in patients with RA with periodontitis.
(Üstün et al., 2013.)	To assess the impact of host modulation treatment of periodontal and biochemical markers.	Longitudinal observation study	TNF- suppression has been proven in studies to enhance clinical outcomes in both RA and periodontitis. One of the underlying reasons for this clinical improvement may be a decrease in IL-1 and IL-8 levels of GCF as a result of anti-TNF medication. Another significant conclusion of this study is that anti-TNF medication reduces GCF volume in periodontitis patients. Previously, an increase in GCF flow was seen as the severity of the inflammation increased.	Current findings from a sample of patients with RA indicate that host modulation can drastically affect the biochemical markers of the periodontium in patients with periodontitis even in the absence of periodontal treatment.
(Kobayashi et al., 2014)	The purpose of this study was to see how an anti-TNF inhibitor (adalimumab) affected the periodontal health of RA patients and to compare serum protein profiles before and after treatment.	Prospective clinical trial	After adalimumab medication, there was a substantial reduction in GI, BOP, probing depth, DAS28-CRP, and serum TNF- and IL-6 levels.	These findings might lead to a positive effect of adalimumab treatment on the periodontal health of patients with RA.

Adalimumab since they bind to both sTNF-a and mTNF-a (Xu et al., 1999). Further, Etanercept does not induce T lymphocyte apoptosis in the lamina propria (Van den Brande et al., 2003). Etanercept has shown good efficacy in rheumatoid arthritis, and its indication has now been extended for use in many other rheumatoid disorders, although long studies

Table 4 PICO table.

Population being studied	Autoimmune patients with any type of autoimmune disease, age, sex, gender, and severity. The population is not restricted to any geographic area; papers will be examined all around the world.
Intervention	Autoimmune patients that are being treated with biological treatment, anti-TNF-a.
Comparison group	Normal patients with periodontitis, other autoimmune patients that are using different treatments, and normal people.
Outcome of interest	Prevalence of osteonecrosis following surgical intervention, and degree of periodontium health after drug administration.
Setting	Self-care at home.
Study Design	Systematic Review

Table 5 Abbreviations.

Abbreviations	Meaning
TNF	Tumor necrosis factor
Anti-TNF-a	Tumor necrosis factor alpha inhibitors
IgG1	Immunoglobulin G1
DMARDs	Disease-modifying antirheumatic drugs
IL-1	Interleukin-1
IL-12	Interleukin-12
IL-13	Interleukin-13
Anti-IL	Interleukin inhibitors
MMP-8	Matrix metalloproteinase-8
MMP-9	Matrix metalloproteinase-9
FDA	US Food and Drug Administration
mAb	Monoclonal antibody
RA	Rheumatoid arthritis
PD	Periodontal disease
AI	Autoimmune
GI	Gingival index
ONJ	Osteonecrosis of the jaw
OM	Osteomyelitis
MRONJ	Medication-related osteonecrosis of the jaw
PI	Plaque Index
CAL	Clinical Attachment Loss
BOP	Bleeding on probing
RANKL	Receptor activator of nuclear factor kappa-B ligand
DRONJBRONJ	Denosumab-related osteonecrosis of the jawsBisphosphonate related osteonecrosis of the jaw
IBD	Inflammatory bowel disease
GCF	Gingival crevicular fluid
DAS28-CRP	Disease Activity Score-28-C-reactive protein
AS	Ankylosis spondylitis
PsA	Psoriasis, psoriatic arthritis

must be performed to test its efficacy, as Etanercept was not effective in Crohn's disease (Sandborn et al., 2001). Following this achievement, Adalimumab (Humira), a fully human recombinant immunoglobulin G1 monoclonal antibody (IgG1), was designed to inhibit tumor necrosis factor-alpha (TNF-a or TNF) which is being used in long-term treatment courses. The unique character of mAb is its monospecificity since it detects just one antigenic determinant (called an epitope) in a given molecule (Dübel, 2007).

4.1.2. TNF significance

In the body, TNF is a protective agent against infection and injury through multiple biologic mechanisms, as it activates some mediators in both innate and adaptive immunity (Tsuchiya et al., 2016). It is essential for embryonic development, the sleep-wake cycle, lymph node follicle creation, and germinal centre formation, among other things like activating the osteoclast (Dübel, 2007). Additionally, TNF not only stimulates the generation of inflammatory cytokines, but also improves endothelial cell adhesion and permeability, as well as the recruitment of immune cells such as neutrophils, monocytes, and lymphocytes to inflammatory areas (Yang et al., 2018). Despite its critical protective role, it can cause cell apoptosis and necrosis under specific conditions, leading to bone damage. This can be implicated in several pathological approaches such as rheumatoid arthritis, ankylosis spondylitis, psoriatic arthritis, and inflammatory bowel disease, in which serum TNF-a levels are high in the patients (Osta et al., 2014). Thus, blocking TNF-a will stop inflammation and joint destruction by using it alone or in conjunction with other medications (Romas & Gillespie, 2006).

4.2. Immunotherapy and dentistry

This has a beneficial role in reducing bone resorption too, by inhibiting osteoclast differentiation and activation in periodontitis patients as well as autoimmune patients, compared to periodontitis patients not on TNF-a antagonists, resulting in the lowering of soft-tissue breakdown, inhibition of bone, and periodontium degradation (Assuma et al., n.d.). Zamri and de Vries (2020) reported not only a significant reduction in pocket depths and clinical attachment loss, as well as bone resorption in autoimmune patients who received these medications, but also increased gingival index and bleeding at probing after 30 days of taking them, and since anti-TNF-a is used in the treatment of chronic diseases, treatment periods are always longer than 30 days.

4.2.1. Animal clinical trials

Similarly, in an experiment on mice, Sakunrangsit et al. (2021) found that Etanercept is effective in preventing mandibular cancellous and cortical bone loss when subjects were introduced to periodontitis and other inflammatory mediators. Another study (Assuma et al., n.d.) on animals also concluded that the injection of IL-1 and TNF blockers inhibited periodontal bone loss by 60%, but also increased gingival inflammation.

4.2.2. Human-based findings

These statements coincide with the results we reviewed from the other articles listed in Table 3, which are close to a collective result of the effectiveness of anti-TNF-a medications in the treatment of AI disorders, reduction of bone loss, and CAL in patients with PD with one or more AI diseases, besides peri-

odontal therapy (Kudo et al., 2014); however, it slightly increased the incidence of gingivitis in these patients. As known, ongoing gingivitis can eventually cause periodontitis (Lang et al., 2009). This may be one of the many side effects of anti-TNF-a, which warrants further research on anti-TNF-a treatments.

4.3. Oral implication of immunotherapy

Another reported major adverse effect of the drugs was osteonecrosis (Cassoni et al., 2016). Since TNF-a and receptor activator of nuclear factor kappa-B ligand (RANKL) share some biological features, and RANKL suppression by denosumab is linked to medication-related osteonecrosis of the jaw (MRONJ), TNF-a inhibition may be associated with MRONJ (Brijs et al., 2020). Denosumab is a type of monoclonal antibody that works on inhibiting RANK proteins. Normally, RANKL binds to a RANK receptor in preosteoclasts, causing them to mature into osteoclasts, osteoclast activation, and survival. Inhibiting this interaction subsequently prevents bone degeneration, and since RANKL and TNF-a both belong to the TNF superfamily and play a role in immune homeostasis and bone degradation, blocking TNF-a may result in the same effect as blocking RANKL, thus potentially causing MRONJ (Brijs et al., 2020).

4.3.1. Periodontium health and TNF-a

Since TNF-a is also responsible for osteoclast formation that is needed for bone remodeling, healing, and regulating immune cells, blocking it could have a catastrophic effect on bone healing and host response, leading to an increased risk of infection and little to no bone repair. The result of these chain reactions is the explanations found for osteonecrosis in the studies listed in Table 2. A randomised clinical trial on rats (Ferreira-Junior et al., 2020) suggested that TNF-a inhibitors can change bone capacity because inhibiting TNF-a will also inhibit proliferative and remodeling inflammatory steps, as well as alter osteoblastic differentiation. The study also noted fewer bone fillings after tooth extraction. While many authors agreed with Ferreira, some, on the other hand, added infection as another cause of osteonecrosis after intervention (Cassoni et al., 2016). Our review found that patients on anti-TNF-a developed osteonecrosis following dental extractions, implant placement, trauma, endodontic surgery, poorly fitting prosthesis, and titanium plates fixation, which are all considered causal factors (Amigo-Basilio et al., 2021). Based on those findings, anti-TNF-a might be considered a risk factor for osteonecrosis. However, all patients had a full recovery after surgical treatment that included implant removal and deep debridement, followed by a long and intensive course of systematic antibiotics, analgesics and steroids, and continuous irrigation after discharge (Amigo-Basilio et al., 2021), (Cillo & Barbosa, 2019). Almost all the patients had to stop their TNF-a inhibitor medications and replace them with other temporary options, making their systematic illness unstable for a while. Therefore, a regular dental check-up is strongly recommended before and during anti-TNF-a therapy to prevent any complications. It is also necessary for the dentist and the physician to communicate and work in coordination in the treatment journey for these patients.

Due to the limited data and studies on these drugs, further clinical studies and trials are needed to identify and record the occurrence of osteonecrosis in patients treated with biological drugs, and their long-term effect on periodontal structures, to further establish the incidence, investigate causality, and generalise the results.

5. Conclusions

TNF-a plays a primary role in the regulation of immune mediators, the activation of bone remodeling, and resorption pathways. Hence, blocking it has positive outcomes in treating autoimmune diseases. It is also beneficial in treating periodontitis by lowering bone resorption rates. However, it increases gingivitis slightly and could promote osteonecrosis after a dental intervention. Patients taking TNF-a inhibitors should be clinically investigated by a dentist before starting treatment and should be carefully monitored for osteonecrotic lesions of the jaw, especially after dental procedures or during periodontal disease. Further clinical studies showing the long-term effect of anti-TNF-a *vis-a-vis* dentistry must be carried out by future researchers since there is a paucity of clinical studies on human samples.

6. Institutional review board statement and number

Approved vide FUGRP/2021/254/634/616. This review was held at Riyadh Elm University- Saudi Arabia- Riyadh-Namuthajiyah campus.

CRediT authorship contribution statement

Rana Majdi Abunemer: Conceptualization, Methodology, Writing – original draft, Visualization. **Rakan Saifuddin Shaheen:** Conceptualization, Writing – review & editing, Supervision. **Renad Abudullah Alghamdi:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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