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The Biologic Therapy "Rituximab": Its Uses in Oral Medicine and Adverse Oral Effects: A Narrative Review

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ABSTRACT

Rituximab is an anti-CD20 monoclonal antibody that targets B lymphocytes, reducing antibody production. As a result, it is widely used to treat lymphomas, leukemia, and autoimmune diseases. This review aims to discuss the applications of rituximab in treating oral diseases and to highlight its potential adverse effects. It also summarizes guidelines from publications on managing patients receiving biologic therapies, including rituximab.

A search of PubMed, Medline, Web of Science, Scopus, and Google Scholar was conducted using terms, such as rituximab, oral manifestations, adverse effects, periodontitis, gingivitis, autoimmune disease, and dental considerations. Case studies, case reports, and reviews with no publication date restrictions were included.

The literature supports rituximab's effectiveness in managing oral lesions associated with autoimmune conditions, like pemphigus vulgaris, mucous membrane pemphigoid, paraneoplastic pemphigus, lupus erythematosus, and Behçet's disease, using doses similar to lymphoma or rheumatoid arthritis protocols. However, its effectiveness for recurrent oral aphthous ulcers is not well established. Rituximab also shows promise in improving salivary gland function and reducing antibody titers in patients with Sjögren's syndrome. Clinical reports have shown success in treating refractory cases of desquamative gingivitis, periodontitis, oral lichen planus, and vasculitis. Nevertheless, oral adverse effects have been reported, with medication-related osteonecrosis of the jaws (MRONJ) being the most severe side effect. Other side effects include oral lichenoid reactions observed in lymphoma cases treated with rituximab and infections caused by fungi, viruses, and bacteria. Animal studies indicate that rituximab can impair wound healing.

There is a lack of standardized guidelines for the dental management of patients on rituximab therapy; available information is based on clinical experiences of physicians and surgeons. Dental professionals should be aware of the increased bleeding risk in these patients and eliminate all potential risk factors for MRONJ. For patient safety, individuals receiving rituximab should be under the supervision of a healthcare professional, such as a dentist or an oral medicine specialist experienced in managing biologic therapies, both before and after treatment.

Keywords: Rituximab, Oral manifestations, Adverse effects, Dental considerations, Dental management.

1. Introduction

Biological therapies, as defined by the US Food and Drug Administration (FDA), are any virus, therapeutic serum, toxin, antitoxin, or similar product applicable to the prevention and treatment of human diseases (1). This new class of therapeutic agents was recently introduced to the medical world and proved to be helpful in the treatment of some serious medical conditions, such as

autoimmune diseases and cancers. The main types of biological therapies are classified into anti-tumour necrosis factor-alpha (TNF-α) inhibitors, anti-interleukin (IL) therapies, anti-integrin inhibitors, anti-B cell inhibitors; and anti-T cell inhibitors (2). Rituximab belongs to the class of anti-B cell inhibitors, also known as monoclonal antibodies (3).

The benefit of biological therapies cames from their ability to potentiate the immunosuppressive agents or even replacing them with relatively minimal side effects compared to other immunosuppressive agents. In addition, they can enhance the anticancer immune response or prevent the cancer cell signals against the immune system (2).

Rituximab is a laboratory-produced monoclonal antibody that specifically targets a protein (antigen) called CD20, which is found on the cell wall surface of B lymphocytes. By binding to CD20, rituximab specifically triggers the destruction of these cells and subsequently suppresses the corresponding antibody production, while it does not affect the plasma cells, which are devoid of this antigen. Therefore, rituximab is widely used for the management of lymphomas, leukemia, and autoimmune diseases (4). Studies also demonstrated the efficacy of rituximab in managing T-cell-mediated immune diseases through its immunomodulation of lymphocyte function, thereby suppressing cytokine production (3,4). Rituximab is delivered by infusion in one of two protocols. The lymphoma protocol (given for lymphoma or autoimmune disease) is of four weeks of 375mg/m^2. The rheumatoid arthritis (RA) protocol is of two weeks of 1000mg every other week, and the dose can be repeated every six months (5).

The oral adverse effects of biologic therapies vary according to the agent used (6,7), rendering their review lengthy and confusing for the general dental practitioner (8). Therefore, focusing on a single medication at a time can be more useful for the reader. Since rituximab is known for being the most widely used and effective biologic agent for the management of autoimmune vesiculobullous disease affecting the oral mucosa (9), this review was designed to review this agent from an oral medicine perspective.

Due to the superior characteristics of rituximab in terms of efficacy, lower side effects, and specific target, the prescribing of this drug is surging, making it the most widely used compared to conventional therapies for autoimmune diseases and cancers, especially in the management of some diseases with oral manifestations and of great concern for dentists and oral medicine specialists for managing diseases, such as pemphigus vulgaris, mucous membrane pemphigoid, lupus erythematosus, Behcet's disease and Sjögren's syndrome, paraneoplastic pemphigus, among other autoimmune diseases (7). In addition, rituximab therapy can produce adverse effects that impose a significant impact on the safe dental management and the oral health care of patients (3,7); some of them are serious and are counted as oral toxicity to the drug (10). Therefore, dentists and oral health providers should be aware of the uses of rituximab in the management of oral diseases and the implications of this drug in the dental management of patients, in addition to its adverse effects on the oral cavity.

This narrative review aims to give an overview of rituximab uses in the field of oral medicine for the management of oral diseases, in addition to the oral adverse effects associated with rituximab therapy. In the absence of standardized, universally accepted guideline for the dental management of patients on biologic therapy, this review also aims to summarize the suggested guidelines derived from publications reporting management of patients on biologic therapies, including rituximab.

2. Methods

For this review, a systematic online search was performed using PubMed, Medline, Web of Science, Scopus, and Google Scholar databases. The search included the following terms in titles and abstracts: rituximab, oral manifestations, oral mucosa, adverse effects, periodontitis, gingivitis, autoimmune disease, infections, and dental considerations. The literature search covered the period from June 2025 to August 2025. The inclusion criteria comprised 1) English-language publications were included, with no restriction on publication date, 2) Case reports or case series studies, 3) Recent narrative reviews, systematic reviews or meta-analysis publications.

3. Results

3.1 Rituximab Use in the Treatment of Oral Disease

3.1.1 Mucocutaneous Autoimmune Diseases

3.1.1.1 Oral Lichen Planus

Oral lichen planus (OLP) is a chronic immune-

mediated disease of unknown cause that affects the skin, oral mucosa, genitalia, scalp, and nails. OLP is more frequently observed and follows a more prolonged course compared to skin lesions (11).

The standard treatment for erosive OLP primarily involves immunosuppressive agents, such as corticosteroids, cyclosporine, azathioprine, and tacrolimus, although some cases are resistant to these therapies (12). Parmentier et al. (2008) were the first researchers to report successful treatment of mucocutaneous lichen planus, including the oral mucosa, which did not respond to steroids or tacrolimus, using a 3-month course of rituximab (13). Subsequently, Heleen et al. (2015) described a case of erosive lichen planus unresponsive to corticosteroids and tacrolimus that responded quickly to rituximab, resulting in long-term remission (14). Lagerstedt et al. (2022) documented a case of severe oral and vulvovaginal lichen planus treated unsuccessfully for 20 years with ultra-potent corticosteroids, methotrexate, and hydroxychloroquine, but effectively managed with rituximab (15). However, one report noted the failure of rituximab to control mucocutaneous erosive lichen planus in four patients (16).

On the other hand, Mannu et al. (2025) reported a case of lichen planus that occurred in a patient with mucocutaneous pemphigus vulgaris, who was treated with prednisolone and rituximab infusion following an RA protocol (17). It is worth noting that there are a few reports of the coexistence of pemphigus vulgaris and lichen planus (18,19), with evidence suggesting that regulatory T (Treg) cells may play a role in the pathogenesis of OLP and pemphigus vulgaris (PV) (20). This may raise questions about the validity of reported rituximab-induced lichen planus in patients with pemphigus vulgaris who have received rituximab treatment (17).

Rituximab is not the sole biologic therapy used for managing refractory erosive OLP. Various biologic treatments, such as anti-CD2, anti-TNF-α, anti-IL2, anti-IL17, anti-IL12/23, and anti-IL23 agents, have been effectively employed. Interestingly, some reports have noted the development of OLP during the treatment with TNF-α inhibitors (21).

Rituximab is not a first-line or standard treatment for OLP. It should only be considered for treating OLP in severe, resistant cases that do not respond to conventional immunosuppressive therapies.

3.1.1.2 Pemphigus Vulgaris

Pemphigus Vulgaris (PV) is a serious autoimmune mucocutaneous blistering disease characterized by the production of antibodies by B lymphocytes, targeting desmosomal proteins (desmoglein 1 and desmoglein 3), which results in intra-epithelial split. It presents clinically as short-lived large bullae that, when ruptured, leave denuded areas with a prominent Nikolsky sign. Although this disease is relatively common in the Middle East, epidemiological studies in Jordan are lacking, but approximately 15 new cases are reported annually (22).

Traditionally, PV is effectively treated with corticosteroids, which, when used long-term, are linked to many side effects. The later development of steroid-sparing agents, such as azathioprine and mycophenolate mofetil, has enabled the reduction or cessation of corticosteroids (3). The advent of rituximab has significantly advanced the management of PV by enabling a precision approach that targets the production of the pathogenic antibodies (11,17,23). Nevertheless, rituximab is still frequently administered alongside prednisolone to achieve a lower dose of the immunosuppressive drug and to reduce adrenal suppression (23,24). Clinical studies and case reports have documented a decrease in anti-desmoglein 3 titers and B-lymphocyte depletion following rituximab therapy (23,25). Currently, it is regarded as the first-line treatment for PV (26), and a better prognosis can be achieved if rituximab is administered within the first six months of disease onset (27).

For the treatment of PV, rituximab is typically administered by infusion at the RA dose (28). There are reports of successful treatment of oral lesions in three PV patients using two 5 mg/cm^2 intra-lesional rituximab injections, spaced two weeks apart (29,30). This administration method has advantages over infusion, as it avoids the adverse effects associated with IV delivery and the lower dose reduces treatment costs. Unfortunately, disease relapse was observed in up to 20% of patients treated with this method (25,29). Rituximab should be used as a first-line therapy for refractory oral PV due to its high efficiency, steroid-sparing advantage and diagnosis improvement.

3.1.1.3 Mucous Membrane Pemphigoid

Mucous membrane pemphigoid (MMP) is an autoimmune mucocutaneous vesiculobullous disease

mainly affecting mucous membranes, including the oral mucosa and, less often, the skin. The autoantibodies specifically target antigens in the basement membrane zone, primarily collagen XVII (BP180), BP230, laminin-332, and integrin, causing subepithelial blisters that eventually ulcerate and heal with fibrosis and scarring (31). While the effectiveness of rituximab in PV has been thoroughly studied, limited data exists regarding its potential role in treating pemphigoid diseases.

In 2021, the European Academy of Dermatology and Venereology (EADV) guidelines categorized MMP into mild to moderate and severe forms. The mild to moderate type is confined to the oral mucosa, with or without skin involvement, while the severe type involves extra-oral or skin sites. Rituximab was recommended only as a second-line treatment for severe MMP and as a third-line option for mild to moderate cases unresponsive to standard immunosuppressive (32,33). Initiating rituximab early appears to enhance the disease prognosis by preventing scarring of the healing MMP ulcers (34). Clinical outcomes were significantly better in patients treated with the lymphoma protocol than the RA protocol (35).

Several case reports published over the past decade have documented positive responses to rituximab as an adjunct therapy in treatment-resistant cases of MMP (36,37), although with varying degrees of success (26).

Lytvyn et al. (2022) published a systematic review on biologic treatment outcomes in MMP, including data from 63 studies. They compared the results of treatment with rituximab (112 patients), intravenous immunoglobulin (154 patients), and TNF-α inhibitors (only 7 patients). They reported complete remission of the disease in 70.5%, 61.7%, and 71.4% of the patients, respectively (38). Notably, two patients treated with rituximab died due to severe infections. Baffa et al. (2022) reported disease control in 80% of their patients (n=10) within 8 weeks after at least one cycle of rituximab therapy, while 20% were non-responsive. They noted that rituximab was effective and safe for patients with MMP (39). One study comparing the response of different bullous diseases (MMP, linear IgA disease, epidermolysis bullosa aquisita, and bullous pemphigoid) found that MMP was the most responsive (40).

In a French retrospective single-center study involving 109 patients with MMP who did not respond to conventional immunosuppressive therapy, rituximab infusions (1g administered 14 days apart, repeated every six months) were given alongside immunomodulatory drugs, such as dapsone and salazopyrine. Complete disease remission was achieved in 85.3% of the studied patients after two cycles of rituximab, but this percentage decreased to 68.7% after one year (41). A more recent Australian retrospective cross-sectional study of 45 patients found that, among those who received rituximab (1g given intravenously on days 1 and 14) and were followed up for at least six months, 97% achieved complete remission after a single course without major adverse effects (42) Conclusively, rituximab as an adjuvant therapy with corticosteroids results in rapid, complete, and long-lasting remission of PV (24) and MMP (43).

3.1.1.4 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder that affects multiple body systems and is characterized by the production of antinuclear antibodies. A recent meta-analysis reported a 31% prevalence of oral mucosal lesions in SLE patients, with 30% showing oral ulcers.(44) Rituximab has proven to be effective in treating severe cases of SLE, especially when combined with other immunosuppressants (45,46).

Bullous systemic lupus erythematosus (BSLE) is a rare variant of SLE marked by the sudden appearance of tense, sub-epidermal, fluid-filled blisters mainly affecting mucous membranes, particularly the oral mucosa, which often heal without scarring. It is more common in women in their 20s to 40s, with the highest prevalence among individuals of African descent. Typical treatments include systemic steroids, immunosuppressants, like mycophenolate mofetil, and dapsone, with varying levels of success (47). Off-label use of rituximab has yielded positive results in refractory BSLE cases (47-49). The recommended dosing generally involves two infusions of 1,000 mg each, spaced two weeks apart.(47, 48) Rituximab works by depleting mature B-cells that are CD20-positive, likely decreasing circulating anti-type VII collagen antibodies responsible for blister formation in BSLE patients (46).

While it is not always a first-line treatment, rituximab can be beneficial in refractory cases of SLE.

3.1.1.5 Desquamative Gingivitis

Desquamative gingivitis (DG) is a clinical diagnosis characterized by painful desquamation, vesicles, atrophy, or erosion, accompanied by diffuse erythema of the marginal and attached gingiva. It may be the early or sole clinical sign of various diseases, including erosive lichen planus, pemphigus, MMP, lupus erythematosus, and allergic reactions (50). Clinical reports described rituximab as an effective adjunct therapy for refractory DG caused by PV (24) and MMP (43,51). The recommended treatment involves two infusions of 1000 mg each, spaced two weeks apart (43).

3.1.1.6 Paraneoplastic Pemphigus

Paraneoplastic pemphigus (PNP), recently called paraneoplastic autoimmune multi-organ syndrome, is a lethal form of pemphigus associated with an underlying tumor, most often myeloproliferative disorders. Patients typically present with severe and debilitating stomatitis (52).

Paraneoplastic pemphigus is typically a stubborn disease, and the best outcomes have been reported with combined neoplasm surgical removal and high-dose corticosteroids, along with the addition of steroid-sparing agents. Patients who do not respond to this protocol are often managed with rituximab therapy (53). Borradori et al. (2001) reported a 61-year-old female with severe erosive stomatitis and follicular non-Hodgkin lymphoma diagnosed as PNP, and her oral lesions were resistant to several immunosuppressive agents. She received 375 mg/m^2 of monoclonal rituximab once a week for four weeks, which resulted in rapid improvement of oral lesions with re-epithelialization of the oral mucosa (54). Adnani et al. (2022) documented a case of PNP in a patient with abdominal lymphoma. The patient's mucosal lesions were treated and resolved with a combination of intravenous immunoglobulin and methylprednisolone, along with intravenous rituximab (55).

3.1.1.7 Sjögren's Syndrome

Sjögren's Syndrome **(**SS) is a systemic autoimmune disease that affects the exocrine glands and presents clinically as dry mouth, dry eyes, and a connective tissue disease, most commonly RA or lupus erythematosus (secondary SS). When the symptoms are limited to dry eyes and dry mouth, the condition is called primary SS or Sicca syndrome. Primary SS is characterized mainly by dry eyes and dry mouth, but symptoms may include fatigue, joint pain, muscle pain, Raynaud's phenomenon, and multi-organ inflammation of organs, such as the nerves, lungs, kidneys, and liver. It is also associated with a higher risk of developing certain conditions, such as B-cell lymphoma (56).

Oral dryness is a common and bothersome symptom in both types of SS, but is more intense in patients with Sicca syndrome. Recently, rituximab has been recognized as an off-label treatment that effectively manages SS (4,57), and increases saliva secretion in patients who still have some residual salivary gland function, and to alleviate xerostomia in SS patients (58-61) and Sicca syndrome patients (62-67) over an extended period (63). A recent controlled study observed a reduction in autoantibody titers and B-lymphocyte counts in Sicca syndrome patients treated with rituximab, although it did not significantly improve salivary gland function (68). More research is needed to determine whether different clinical types of SS respond differently to rituximab therapy.

Non-Hodgkin lymphoma, which often affects the parotid gland, is a serious complication of both SS and Sicca syndrome, affecting approximately 8%-10% of patients. Patients treated with rituximab have a significantly higher chance of tumor regression and a better survival rate (62,69).

3.1.2 Gingivitis, Periodontitis and Periapical Periodontitis

Most information about the link between rituximab therapy and gingival or periodontal disease comes from reports of RA patients receiving rituximab (70,71). This connection may be explained by the close relationship between RA and periodontal disease, as both share similar biological, pathological, and immunological mechanisms. Both are chronic inflammatory conditions characterized by immune system dysregulation and increased levels of pre-inflammatory cytokines, such as IL-1, IL-6, and TNF-α, which lead to tissue damage. They also share common risk factors, including tobacco smoking, microbial changes, and genetic predisposition (HLA-DRB1) (70). Therefore, rituximab therapy may benefit both RA and periodontitis in RA patients (72).

Coat et al. (2015) conducted a comparative study on the effect of rituximab therapy on the periodontal condition of 21 RA patients divided into two groups, where group 1 received a single dose of rituximab, and

group 2 received two doses. They observed a significant dose-dependent reduction in periodontal pocket depth and clinical attachment loss after approximately six months of rituximab therapy (73). These findings were later supported by the results of a cross-sectional study by Ziebolz et al. (2018) (74), which included 168 RA patients, and by a meta-analysis that included 146 patients from four studies (Zhang et al., 2021) (71) and by reviews (75,76). Conversely, one study on RA patients reported increased potential for periodontal inflammation in patients treated with the combination of rituximab and a TNF-α inhibitor (74).

Periapical periodontitis is thought to be common in patients with chronic inflammatory disorders, and thus, rituximab, which is used in managing these disorders, has been reported to improve the periapical healing of endodontically-treated teeth (75).

3.1.3 Vasculitides Oral Diseases

3.1.3.1 Wegener's Granulomatosis/Granulomatosis with Polyangiitis

Wegener's granulomatosis/granulomatosis with polyangiitis (GPA) is a rare autoimmune, potentially lethal disease associated with anti-neutrophil cytoplasmic antibodies (ANCA) vasculitis. GPA is characterized by vasculitis affecting small and medium-sized blood vessels and the formation of granulomas. It commonly involves the lungs and kidneys, but can also affect the oral mucosa, especially the gingiva and palatal mucosa (77). Oral lesions are reported in 6%-13% of GPA cases, with gingival lesions often being the first sign in 68.4% of those oral cases (78,79). Clinically, it presents as gingival swellings or non-specific ulcerations on the palatal gingiva (80,81). The standard treatment for GPA involves systemic immunosuppressants, such as corticosteroids and/or cyclophosphamide or azathioprine. Rituximab has been reported as an effective therapy for systemic and oral lesions of GPA (82,83).

3.1.3.2 Behcet's Disease

Behcet's disease **(**BD) also known as Behcet's syndrome, is a chronic disease involving multisystem vasculitis. The typical clinical presentation includes a triad of recurrent oral and genital ulcers and uveitis. The clinical features may also encompass joint, mucocutaneous, eye, neurological, vascular, and gastrointestinal symptoms that can fluctuate between exacerbation and remission. The incidence of BD in Jordan is believed to be among the highest globally, affecting approximately 66 in 10,000 people, especially in the northern region of the country (84).

The traditional treatments for BD include glucocorticoids, colchicine, and dapsone (85). Rituximab was first used for managing BD in 2010 (86). Although TNF-α inhibitors are the most commonly used biologic therapy for BD control, several reports have reported the effectiveness and safety of rituximab in RA protocol dose in managing the disease (1,87,88). The surface of B lymphocytes, especially memory cells, has an altered antigen that correlates positively with BD activity (89). Rituximab targets the entire lineage of B lymphocytes with CD20 receptors, except for plasma cells. It also reduces antigen presentation and cytokinemia by inhibiting T-cell activity (88). Nonetheless, rituximab's effectiveness for recurrent oral aphthous ulcers is not well-established (11).

Mohta et al. (2022) reported a case of BD in a 34-year-old female patient who was undergoing treatment with various medications, including systemic steroids, colchicine, cyclophosphamide, and dapsone, with varying responses and multiple recurrences (88). The patient's treatment with rituximab, following the RA protocol, led to the healing of all existing lesions with no recurrence over the following year. However, rituximab is considered a second-line therapy for controlling BD when it fails to respond to conventional treatment with colchicine (87).

3.1.3.3 Giant Cell Arteritis/Temporal Arteritis

Giant cell arteritis (GCA) is the most common idiopathic systemic vasculitis that affects large and medium-sized blood vessels, such as the aorta and carotid artery. Typically, it affects patients over 50 years old. It commonly involves the temporal artery (temporal arteritis) and presents as a throbbing, continuous headache on one or both sides of the forehead, jaw pain, especially during chewing, fatigue, fever, and most seriously, vision disturbances that can progress to blindness. Glucocorticoids have long been the gold standard treatment for GCA (90).

Early in this century, Bhatia et al. were the first researchers to successfully treat a case of GCA using rituximab as an adjunct to methylprednisolone and cyclophosphamide (91). Later, Mayrbaeurl et al. managed to treat GCA solely with rituximab (92).

Conversely, Mulhearn et al. (2021) reported a case of GCA that was refractory to rituximab, but responded favorably to another CD20 inhibitor, tocilizumab (93). This was explained by the immunological heterogeneity of GCA with different immunophenotypes of the disease that respond to different types of biologic therapies.

Since the rituximab efficacy in the management of GCA is not well-established, with inconsistent results from case reports, rituximab is not a standard treatment for GCA, though it may be considered for specific refractory cases.

3.2 Oral Adverse Effects/Toxicity of Rituximab

3.2.1 Oral Lichenoid Drug Reaction

Oral lichenoid drug reaction (OLDR) is a recognized pathological condition that can affect the skin, oral mucosa, or both simultaneously. OLDR and oral lichen planus are almost indistinguishable clinically and histologically. Oral lichen planus has an unknown cause, while OLDR is an allergic reaction to certain dental restorative materials and several commonly used chronic medications, such as oral hypoglycemic agents, antihypertensive drugs, and non-steroidal anti-inflammatory agents. It is usually managed by stopping or replacing the responsible drug, although complete clinical resolution may require the use of topical or systemic steroid therapy (94). OLDR occurs when a drug acts as a hapten and binds to the keratinocyte cell wall, triggering a cytotoxic T-cell response (95). A standardized, universally accepted set of criteria for diagnosing OLDR is still debated and presents a challenging issue.

Oral lichenoid drug reaction has been recently recognized as a potentially malignant disorder, with a surprisingly wide and variable malignant transformation rate ranging between 0.4% and 12.5% (96).

Kuten-Shorrer et al. in 2014, reported the first case of rituximab-induced OLDR in a lymphoma patient after a high dose of the drug (750mg/m^2) (97). Subsequently, several reports anecdotally described the emergence of OLDR related to rituximab therapy, primarily for B-cell non-Hodgkin's lymphoma (10,98-100). The appearance of OLDR may be delayed up to 3 months after rituximab therapy (98).

Confusingly, dermatologic and oral lichenoid lesions have been reported in some hematologic malignancies, possibly due to anti-tumor immune reactions, even before the initiation of immunotherapy (101). However, the key to diagnosing a drug-induced lichenoid reaction is the temporal relationship between lesion onset and drug administration, as well as the resolution of the lichenoid lesion after the therapy session (95). When severe symptomatic OLDR occurs, biologics and corticosteroids may be used to alleviate symptoms (10).

3.2.2 Retardation of Oral Traumatic Ulcer and Wound Healing

Oral traumatic ulcer is not an immune-mediated condition. The healing of traumatic ulcers was impaired in Wister rats treated with different doses of rituximab compared to control animals, and this was attributed to reduced inflammatory cell migration and decreased acute inflammation in the treated animals (102). The same scenario may apply to the reported impaired healing of surgical wounds in patients treated with rituximab (6).

3.2.3 Infections

Although considered a safe agent, rituximab increases the risk of systemic infections, such as pneumocystis pneumonia, cytomegalovirus infection, fungal infections, and reactivation of latent hepatitis B-virus infection (6). These adverse effects are mainly due to the drug's immunosuppressive action, along with neutropenia and thrombocytopenia caused by the drug (103). Data collected during the COVID era showed that patients receiving rituximab therapy are at a higher risk of experiencing severe outcomes from COVID-19 (104).

3.2.3.1 *Candida* Infections

Theoretically, the immunosuppressive characteristic of rituximab qualifies it as a risk factor for developing opportunistic infections, such as candidosis (105). Clouse et al. (2019) reported fungal infections in 25% of patients who underwent intestinal transplants and received rituximab as part of their immunosuppression protocol (106). In a retrospective study on kidney transplant patients who developed oral/oesophageal candidosis, rituximab therapy was a risk factor for severe infections that required hospitalization (107). However, possibly due to the selectivity of rituximab's immunosuppressive action, the incidence of fungal infection in these patients is relatively low compared to traditional immunosuppressive agents (105). It may be difficult to directly attribute fungal infections to the

CD20 inhibitors, considering the effects of concomitant immunosuppressive therapies (107,108). More research is needed on the impact of rituximab therapy on oral *Candida* colonization and infection.

Oral candidosis is not particularly common among patients receiving rituximab, which selectively depletes the humoral immune system, possibly because the cellular immune system is the primary protective mechanism against candidosis rather than the humoral immune system (109). In any case, clinicians should carefully monitor these patients for the development of these infections, especially when other risk factors, such as denture use, other concomitant immunosuppressive therapy, or diabetes mellitus, are present.

3.2.3.2 Herpes Infections

Clinical studies indicated an increased risk of herpetic infections associated with rituximab therapy, either as a primary disease or reactivation of latent virus (110,111). Luna et al. (2020) reported a higher prevalence of herpes simplex infections among patients with multiple sclerosis treated with rituximab (23.5%) compared to healthy control subjects (9.3%) (112). Additionally, reactivation of latent herpes virus that caused herpes labialis was reported in 30% of patients with pemphigus vulgaris treated with rituximab (113). On the other hand, rituximab therapy in kidney transplant recipients did not appear to affect the development of herpes zoster after transplantation, possibly due to the lower dose of rituximab given to those patients (114).

The relationship between herpetic infections and rituximab therapy cannot be definitively determined whether it is due to the medication or due to the underlying medical condition. As a protective measure, one study recommended that patients scheduled to undergo rituximab treatment get vaccinated against herpes zoster infection (115).

3.2.3.3 Oral Tuberculosis

RA patients treated with TNF-α inhibitors have an increased risk of infection with *Mycobacterium tuberculosis*. Extra-pulmonary tuberculosis has been reported infecting the tongue (116), the tonsillar area (117), and oral mucosa (118) in RA patients on TNF-α inhibitor therapy. Literature searches have not found any reports of oral tuberculosis related to rituximab therapy. Since rituximab may theoretically increase the risk of reactivating latent tuberculosis infection, it is recommended that patients scheduled for biologic therapy, including rituximab, be screened for latent tuberculosis infection. Screening includes evaluation for current or past tuberculosis infection through patient history, tuberculin skin test, and chest radiography (117,119).

3.2.4 Medication-Related Osteonecrosis of the Jaws (MRONJ)

Medication-Related Osteonecrosis of The Jaws (MRONJ) is a rare, but serious, form of osteomyelitis affecting the jaws that develops as a complication of anti-resorptive (bisphosphonates) or anti-angiogenic (denosumab and bevacizumab) medications (120). Recently, other medications, either directly or indirectly, have been associated with the development of MRONJ, including rituximab, although the strength of the evidence remains uncertain (121-124).

The relationship between rituximab and MRONJ remains uncertain, but may be attributed to the supposed anti-angiogenesis effect of the rituximab (125). Javelot et al. (2020) reported a case of MRONJ in an RA patient medicated by risedronate (bisphosphonate), systemic corticosteroids, and rituximab, who developed MRONJ following an acute herpetic infection. They suggested that rituximab-induced immune suppression triggered the herpetic infection, which then caused MRONJ (123). However, the risodronate effect cannot be excluded. Several herpesvirus infections, such as Human Simplex Virus, Cytomegalovirus, and Varicella Zoster Virus, have been associated with rituximab therapy due to the rapid depletion of B lymphocytes, leading to lymphopenia and hypogammaglobulinemia (126).

RA is one of the medical conditions reported as being a risk factor for MRONJ, and it is also commonly treated with rituximab (127). Accordingly, the reported MRONJ cases in RA patients treated with rituximab may have been induced by the underlying disease rather than by the therapy (123,124). More research is necessary to clarify the role of rituximab, if any, in the development of MRONJ. Proper identification of the range of risk factors and associated medications is crucial for prevention, early diagnosis, and effective management of at-risk patients.

3.3 Dental Considerations in Patients on Rituximab Therapy

With the widespread use of biologic therapy, it is

common to encounter patients seeking dental treatment; hence, the dentist and dental team should be capable of safely and properly managing these patients. The well-being of such a patient is a shared responsibility between the dentist and the treating physician. Table 1 summarizes the dental considerations for patients planned for or on rituximab therapy. Rituximab appears to be a relatively safe drug in terms of dental prescription. Muñoz-martínez et al. (2021) reviewed biologic agents and related drug interactions and reported no significant interactions of rituximab with drugs used in dentistry (128).

Table 1. Dental considerations in patients on rituximab therapy

Before starting rituximab treatment	During rituximab treatment
Patient education about: • Oral adverse effects of the medication • Oral/denture hygiene and wearing	• Comprehensive oral examination and careful monitoring for the anticipated drug's adverse effects
Comprehensive oral examination for: • Oral candidosis, especially in denture wearers • Odd ulcerations for the possibility of oral TB in patients with a history of TB • Radiography: o Orthopantogram radiographs o Periapical radiographs	**MRONJ:** • All sources of trauma or infections should be eliminated • If extraction, surgery or endodontic treatment is needed o Atraumatic procedure o Rx antiseptic mouthwash and systemic antibiotic o Follow-up
MRONJ prevention: • Endodontic treatment for un-restorable teeth • Treating periapical pathosis • Treating gingivitis/periodontitis • Extraction of teeth of poor prognosis • Eliminating oral trauma	**Lichenoid lesion:** • Biopsy may be needed in case of doubt • Prevent cancer transformation by avoiding tobacco use, alcohol intake, and eliminating oral trauma and other carcinogenic factors • Rx topical steroid for symptomatic lesions
	Oral surgery/dental extraction: • CBC, platelet count, PT, and INR • Atraumatic procedure • Rx antiseptic mouthwash and systemic antibiotics • Discontinuation of the biological agents before oral surgery 4-5 times the drug's half-life • Follow-up
	Drug prescription: Avoidance of drugs metabolized by the liver, such as: • NSAIDs, e.g. ibuprofen, aspirin, and naproxen • High dose, or prolonged use, of acetaminophen • Opioids, e.g. codeine, meperidine, and tramadol

3.3.1 Prior to Rituximab Therapy

It is crucial for the treating physician to refer any patient scheduled for biologic therapy for a detailed oral and dental evaluation. Patients should be educated about the importance of thorough oral hygiene and the risk factors that increase the likelihood of oral infections, especially if they wear dentures. Besides taking a comprehensive medical and dental history, the patient must undergo a full radiographic assessment, including periapical, bite wing, and orthopantomogram radiographs (129).

MRONJ is a serious adverse effect of rituximab, and to prevent it, all sources of infection, such as gingivitis, periodontitis, and periapical pathosis, should be treated before starting rituximab therapy. Endodontic treatment should be completed at least one week prior, and dental extraction should be performed at least 2-3 weeks before initiating biologic therapy (129). Fitting and adjusting removable appliances or any traumatic prosthesis should also be completed before starting the treatment (129).

3.3.2 During Rituximab Therapy

Several reports described liver injury or toxicity in

10%-15% of patients treated by rituximab due to reactivation of hepatitis B or CMV after treatment. Additionally, there have been cases of acute liver failure caused directly by the drug itself, although this is uncommon and reversible (130). Therefore, medications with hepatotoxic effects or those metabolized in the liver, such as NSAIDs and high doses of acetaminophen, should be prescribed with caution during rituximab therapy (7). Trimethoprim-sulfamethoxazole (Bactrim) is an antibiotic that needs to be used cautiously in patients on rituximab. While it may reduce the risk of severe infections, it can also increase the likelihood of adverse events, including acute kidney injury and anaphylactic reactions (131).

The patient's oral mucosa should be examined carefully to identify lichenoid lesions; in such cases, the patient should be advised to avoid any risk factors for oral cancer. Regular check-ups and topical corticosteroids are recommended for symptomatic lesions (96).

To prevent MRONJ development, dentists should avoid invasive or traumatic procedures whenever possible. There is not enough evidence to support temporary drug withdrawal being effective in reducing the risk of MRONJ (132). However, postoperative antiseptic mouthwashes and antibiotics are accepted practices in clinical settings. Antibiotic prophylaxis has been recommended as necessary, particularly for patients with granulocyte counts below 2000/mm^3 (133).

Hematological side effects of rituximab therapy are uncommon and may include neutropenia, thrombocytopenia, and anemia (134). A complete blood count, platelet count, prothrombin time (PT), and International Normalized Ratio (INR) should be performed before any surgical procedure or exodontia. The elective oral surgical procedures should be scheduled at least one month after the last infusion. Additionally, the possibility of temporarily discontinuing rituximab therapy may be discussed with the treating physician (7). While infections are significant adverse effects, there is insufficient scientific evidence to support the use of antibiotic prophylaxis for these patients when undergoing oral surgery, unless MRONJ development is anticipated. In the absence of universal precautions and guidelines, dental management considerations should be individualized, taking into account the urgency of the surgery, other comorbidities, and concurrent immunosuppressive therapy. Elective surgeries are recommended to be postponed until after the completion of biologic therapy. In urgent cases where biologics are interrupted, therapy can be resumed once satisfactory wound healing is achieved and sutures are removed (135).

4. Discussion

The improved understanding of the pathogenesis of immune-mediated diseases has led to a surge in the development of biologic agents, which are known for their ability to directly target specific immunological pathways, cytokines, or proteins involved in the disease process. According to the US FDA, rituximab is officially approved for the management of non-Hodgkin lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis, and microscopic polyangiitis. The drug's other clinical applications are considered off-label use (12).

While rituximab is being used increasingly in debilitating and potentially lethal systemic immune-mediated diseases, such as PV, MMP and vasculitis cases, it still has a limited role in the management of immune-mediated oral mucosal diseases, which can be managed effectively by optimal use of topical and conventional systemic immunosuppressive agents, with analgesic, antiseptic mouth rinses and good oral hygiene. Nevertheless, rituximab is still required in the management of refractory and steroid-resistant lesions. Another limitation of rituximab use is the high cost and the need for a hospital setting for drug administration (3).

This study has an important limitation that should be noted which was implemented by the nature of this "narrative review". Some of the information on oral manifestations or adverse reactions associated with rituximab therapy came from sporadic case reports or case series studies of patients suffering from immune-mediated diseases or myeloid cancers treated with this drug, while prospective, well-designed studies are lacking. This amplifies the need for retrospective, muticenter clinical studies reporting and explaining the pathogenesis of these adverse effects. In addition, more standardization of the medication dose and protocol for the management of oral diseases in needed.

To date, there are no definitive, universally accepted guidelines for the dental management of patients undergoing biologic therapy or their need for

preoperative prophylactic antibiotics. All published recommendations have been based on personal experiences (3,129), largely set by orthopedic surgeons treating RA patients, but cumulative data from oral/maxillofacial surgeons remains lacking. This highlights the need for standardized prospective studies to assess oral adverse effects and to set guidelines for the dental and surgical management of patients undergoing biologic therapy. Even though various general principles of dental and surgical care for rituximab patients were proposed, precise management should be tailored according to each patient, considering the patient's immune status, the drug dosage and the presence of other comorbidities. In addition, the patients who are planned to receive biologic therapy need to be educated about the agents and their side effects. The patient also needs to be screened before drug administration and careful monitoring afterword (3).

Over time, the list of medications posing a risk for MRONJ has grown beyond traditionally recognized drugs, like bisphosphonates and denosumab. Rituximab has recently been added to this list, though with varying levels of evidence (124). Due to the lack of clinical data in single cases or retrospective studies of MRONJ reported with rituximab, it is not precisely clear whether this agent was the single cause of the disease or other concurrent medications or risk factors (124).

Due to the morbidity associated with this condition, especially in immunocompromised or cancer patients, close collaboration between the treating physician and the dentist is essential to prevent this serious complication.

Despite the proved efficacy of rituximab in treating some serious oral diseases, there is still a lack of consensus on the optimum treatment protocol and suitability of patients for drug use. Future research on the use of rituximab for oral diseases is needed to optimize treatment protocols, explore novel delivery methods (such as intra-lesional or oral administration), and define which specific patient populations are most likely to benefit from the therapy.

In conclusion, patients on rituximab therapy need careful monitoring for potential adverse effects and should be managed by specialists experienced in biological therapies.

5. Conclusions

Rituximab's targeted action on CD20 on B cells makes it an effective, selective, and relatively safe immunosuppressant when compared to traditional treatments like steroids. The application of biologic therapies in oral medicine is still in its early stages. Consequently, more well-designed studies are necessary to clarify the oral side effects of rituximab, explore prevention strategies, and identify precautions during dental procedures. Additionally, fostering better collaboration between dental health providers and medical physicians is crucial to ensure proper patient preparation before rituximab treatment, which can help prevent and manage potential oral complications.

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Conflict of Interests

None of the authors of this manuscript has any potential source of conflict of interests, directly or indirectly, that may have influenced the authors' objectivity towards this research.

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