Review

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Biological Therapy and Oral Surgery: Safety Recommendations and Practices

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The integration of biological therapies, including biologics and biosimilars, into the medical practice has transformed the management of numerous chronic inflammatory, autoimmune, and oncological conditions. However, these treatments can pose challenges in oral and maxillofacial surgery due to their potential effects on wound healing, infection risk, and immune responses. This article reviews the most commonly used biological agents and provides safety recommendations for managing patients on biological therapies undergoing oral surgical procedures, such as tooth extractions (including multiple and surgical extractions), implant placement, periodontal and soft tissue surgeries, and the removal of non-cancerous or cancerous growths in the oral cavity. Key considerations include the oral complications associated with biologic treatments, preoperative risk assessment, perioperative timing of biologic administration, and postoperative monitoring to minimize complications. While several professional organizations have issued recommendations on the perioperative management of biological agents, there is currently no specific guidance tailored to dental or oral surgical procedures. This paper aims to explore the existing literature and recommendations regarding the use of biologics in the perioperative period.

Keywords: biological products; immunosuppression therapy; oral surgical procedures

Introduction

Biopharmaceutical products, known as biological drugs, are used to treat chronic autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriasis, ulcerative colitis, Crohn's disease, as well as neurological and degenerative conditions such as multiple sclerosis and some types of cancer [1].

The term encompasses materials from blood products to stem cells and vaccines, but it is most frequently used to refer to gene and cell-based biological agents, often produced through recombinant DNA biotechnology [2,3].

Despite their significant benefits, these drugs can suppress the immune system, raising the risk of oral infections, impaired wound healing, and oral lesions [4–6].

Overview of Biological Medications

Produced through recombinant DNA, biological drugs fall into three main categories (Table 1, Ref. [1,7–12]):

Signaling Proteins (Cytokines): such as interferon α, β, and interleukin 2, are immunomodulators that regulate inflammation and infection responses.

Monoclonal Antibodies (mAbs or moAbs): cloned from immune cells can deliver various agents, such as chemotherapeutic agents, radioisotopes, toxins, or cytokines that act directly on tumor cells.

Fusion Proteins (Soluble Cytokine Receptors or Ligands): genetically engineered molecules that merge segments from different proteins, combining their beneficial functions into a single structure [4,5].

Signaling Proteins (Cytokines)

Cytokines are small proteins secreted by cells that act as important signaling molecules in the immune system. Among these, immunomodulators like interferons and interleukins are key players in modulating the immune system's activity, particularly in response to infections, autoimmune conditions, and cancer [1].

Interferons: interferon α (IFN-α) and interferon β are cytokines that primarily regulate antiviral responses, immune surveillance, and inflammation. They are used in the treatment of viral infections and certain cancers [4].

Interferon α is used in the treatment of hepatitis B and C as well as some cancers like chronic myelogenous leukaemia and melanoma. It works by inhibiting viral replication and enhancing the immune system's ability to fight infections and cancer cells.

Interferon β is used in treating multiple sclerosis (MS). It helps reduce the frequency and severity of MS flare-ups by modulating the immune response and reducing inflammation [5].

Interferon gamma is indicated for the treatment of chronic granulomatous disease and malignant osteopetrosis [5].

Table 1. Types of biological drugs.

Generic name Trade name	Indication	Technology	Mechanism of action
1.Interferons			
Vedolizumab (Entyvio)	Ulcerative colitis, Crohn's disease	Recombinant humanized immunoglobulin G subclass (IgG)1 monoclonal antibody	Binds to $\alpha4\beta7$ integrin and blocks the interaction of $\alpha4\beta7$ integrin with Mucosal Addressin Cell Adhesion Molecule-1 (MAdCAM-1)
Interferon alfa	Hepatitis, leukemia (lymphoid, myeloid, unspecified), melanoma	Polypeptide drug	Anti-viral and immunoregulatory activity
Interferon beta	Relapsing forms of multiple sclerosis (MS)	Polypeptide drug	Antiviral and immunomodulatory effects
Interferon gamma	Chronic granulomatous disease, malignant osteopetrosis	Polypeptide drug	Immunomodulatory effects
2. Antibodies			
2.1. Tumor necrosis factor-alpha (TNF-α) antagonists			
Adalimumab (Humira)	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease	Monoclonal anti-tumor necrosis factor alpha antibody	Inactivating tumor necrosis factor-alpha
Certolizumab pegol (Cimzia)	Crohn's disease, active rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, plaque psoriasis	Fragment of a humanized TNF inhibitor monoclonal antibody	
Golimumab (Simponi)	Rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, ulcerative colitis	Human IgG1κ monoclonal antibody	
Infliximab (Remicade)	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease	Monoclonal anti-tumor necrosis factor alpha antibody	
Etanercept (Enbrel)	Rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis	Recombinant human TNF-receptor fusion protein	
2.2. B-cell depletor			
Rituximab (Mabthera)	Follicular lymphoma, B cell non-Hodgkin's lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis, granulomatosis with polyangiitis (Granulomatosis with Polyangiitis or Wegener's granulomatosis) and microscopic polyangiitis, pemphigus vulgaris	Monoclonal antibody-B-cell depletor	Attach to a B-lymphocyte antigen Cluster of Differentiation 20 (CD20) and induce B-cell depletion

Table 1. Continued.

Generic name Trade name	Indication	Technology	Mechanism of action
2.3. Interleukin inhibitors			
Anakinra (Kineret)	Rheumatoid arthritis, cryopyrin-associated periodic syndromes, familial Mediterranean fever, Still's disease	Human interleukin 1 receptor antagonist	Competitively binding to the interleukin-1 receptor, blocking interleukin-1 (IL-1) signaling and preventing inflammation
Sarilumab (Kevzara)	Rheumatoid arthritis	Monoclonal antibody interleukin-6 receptor blocker	Bind to the IL-6 receptor, preventing IL-6 from activating its signaling pathways and reducing inflammation
Tocilizumab (Roactemra)	Rheumatoid arthritis, juvenile idiopathic arthritis, juvenile idiopathic polyarthritis	Monoclonal antibody interleukin-6 receptor blocker	Bind to the IL-6 receptor, preventing IL-6 from activating its signaling pathways and reducing inflammation
Secukinumab (Cosentyx)	Plaque psoriasis, psoriatic arthritis, axial spondyloarthritis, juvenile idiopathic arthritis, hidradenitis suppurativa	Fully human monoclonal IgG1κ antibody against interleukin-17A	Bind to the IL-17A cytokine, preventing it from interacting with its receptor (IL-17RA), inhibiting pro-inflammatory signaling and reducing inflammation
Ixekizumab (Taltz)	Plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, non-radiographic axial spondyloarthritis	Humanized immunoglobulin G subclass 4 monoclonal antibody against interleukin-17A	Bind to the IL-17A cytokine, preventing it from interacting with its receptor (IL-17RA), inhibiting pro-inflammatory signaling and reducing inflammation
Ustekinumab (Stelara)	Psoriatic arthritis, psoriasis, ulcerative colitis, Crohn's disease	Human immunoglobulin G1 kappa monoclonal antibody directed against interleukin-12 and IL-23	Bind to IL-12 and IL-23 and block their activity
Risankizumab (Skyrizi)	Plaque psoriasis, active psoriatic arthritis, Crohn's disease, ulcerative colitis	Fully humanized IgG1 monoclonal antibody directed against interleukin 23	Attach to interleukin-23 and block its activity
Guselkumab (Tremfya)	Plaque psoriasis, psoriatic arthritis	Human IgG1λ monoclonal antibody that selectively blocks interleukin-23	Attach to interleukin-23 and block its activity
2.4. Janus kinase inhibitors			
Baricitinib (Olumiant)	Rheumatoid arthritis, juvenile idiopathic arthritis, atopic dermatitis (eczema), alopecia areata,	Janus kinase (JAK) inhibitor	Inhibit the actions of JAK1 and JAK2
Tofacitinib (Xeljanz)	Rheumatoid arthritis, psoriatic arthritis, polyarticular juvenile idiopathic arthritis (pJIA), ulcerative colitis, ankylosing spondylitis		

Table 1. Continued.

Generic name Trade name	Indication	Technology	Mechanism of action
Filgotinib (Jyseleca)	Rheumatoid arthritis, ulcerative colitis		
Upadacitinib (Rinvoq)	Rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, atopic dermatitis, ulcerative colitis		
2.5. Epidermal growth factor receptor (EGFR) inhibitor			
Trastuzumab (Herceptin)	Human Epidermal Growth Factor Receptor 2(HER2)-positive breast, gastroesophageal, and gastric cancers	Monoclonal anti-human epidermal growth factor receptor 2 protein antibody	HER2/neu (erbB2) antagonist
Cetuximab (Erbitux)	EGFR-expressing squamous cell cancer of the head and neck, colorectal cancer	Epidermal growth factor receptor-antagonist	Monoclonal IgG1 antibody directed against the epidermal growth factor receptor
2.6. Monoclonal antibodies-anti-coagulant and anti-neo-vascularization agents			
Abciximab (ReoPro)	Prevent ischemic complications in patients undergoing percutaneous coronary intervention, with Unstable Angina Pectoris, Acute Myocardial Infarction	Fab fragment of the chimeric monoclonal antibody 7E3. platelet aggregation inhibitor	Prevent binding of fibrinogen, von Willebrand factor and other adhesive molecules to Glycoprotein IIb/IIIa receptor sites on activated platelets
Bevacizumab (Avastin)	Cancer therapy, age-related macular degeneration	Monoclonal antibody designed to target and inhibit vascular endothelial growth factor (VEGF)	By binding to VEGF, Avastin inhibits angiogenesis
2.7. Monoclonal antibodies-receptor activator of nuclear factor-kappa B ligand blockers			
Denosumab (Prolia)	Osteoporosis Bone Loss due to Cancer Therapy	The monoclonal antibody that inhibits receptor activator of nuclear factor kappa-B ligand	Inhibit receptor activator of nuclear factor κB ligand (RANKL), reducing bone resorption and enhancing bone strength
2.8. Other antibodies			
Vedolizumab (Entyvio)	Ulcerative colitis, Crohn's disease	Recombinant humanized IgG1 monoclonal antibody $\alpha 4\beta 7$ integrin blocker	Blocks leucocyte trafficking from the circulation to the bowel
3. Fusion proteins			
Abatacept (Orencia)	Rheumatoid arthritis psoriatic arthritis juvenile idiopathic arthritis	Immunoglobin Cytotoxic T-Lymphocyte Antigen-4 Immunoglobulin (CTLA-4) fusion protein	T-cell deactivation

Table 1. Continued.

Generic name Trade name	Indication	Technology	Mechanism of action
Alefacept (Amevive)	Chronic plaque psoriasis	Immunoglobin G1 fusion protein combines part of an antibody with a protein that blocks the growth of some types of T cells	Reduction in T lymphocytes, subsets of CD2+ T lymphocytes as well as CD4+ and CD8+ T lymphocytes
Erythropoietin (Epogen)	Anemia arising from cancer chemotherapy, chronic renal failure, etc.	Recombinant protein	Increase differentiation of progenitor cells to red blood cells
Denileukin diftitox (Ontak)	Cutaneous T-cell lymphoma (CTCL)	Interleukin - 2 receptor-directed cytotoxin combination of Interleukin-2 and Diphtheria toxin	Interleukin-2 receptor binder
4. Immunomodulators blocking the action of phosphodiesterase 4			
Apremilast (Otezla)	Plaque psoriasis, active psoriatic arthritis, Behçet's disease	Phosphodiesterase 4 (PDE4) inhibitor	Blocks the action of phosphodiesterase 4

Monoclonal Antibodies

Monoclonal Antibodies – Tumour Necrosis Factor-Alpha Antagonists

Tumor necrosis factor-alpha (TNF-α), a key regulator of inflammation in autoimmune and inflammatory diseases, is targeted by anti-TNF therapies to reduce pain and joint damage in conditions like rheumatoid arthritis, lupus, and psoriatic arthritis [7]. These treatments also lower disease activity in Crohn's disease, ulcerative colitis, multiple sclerosis, pemphigus, and psoriasis. However, TNF inhibitors can weaken immune defenses against infections and malignancies [4].

Adalimumab (Humira) is a recombinant human monoclonal antibody, indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis and Crohn's disease. Adalimumab has a half-life of 12 to 14 days.

Dental surgery can be safely performed 1 to 2 weeks after the last intake [6].

Certolizumab (Cimzia, certolizumab pegol) blocks TNF-α, thereby alleviating inflammation and symptoms in rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, and plaque psoriasis. Common side effects include bacterial and viral infections, eosinophilic disorders, leukopenia, sensory disturbances, hypertension, and hepatitis with elevated liver enzymes. It has a half-life of 11 to 14 days.

Dental surgery can be safely performed 1 to 2 weeks after the last intake [7].

Golimumab (Simponi) is indicated for the treatment of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis. Golimumab's half-life is 12 to 14 days.

Golimumab treatment has been associated with bacterial (sepsis, pneumonia), mycobacterial (tuberculosis), invasive fungal, and opportunistic infections, some fatal, especially in combination with concurrent immunosuppressive therapy.

Dental surgery can be safely performed 1 to 2 weeks after the last intake [7].

Infliximab (Remicade) is indicated for the treatment of rheumatoid arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis, ulcerative colitis, and Crohn's disease. Its half-life is 8 to 10 days.

Dental surgery can be safely performed 2 to 4 weeks after the last intake [7].

Etanercept (Enbrel) is used to treat rheumatoid arthritis, plaque psoriasis, and ankylosing spondylitis. With a half-life of 70 hours, the usual dose is 50 mg subcutaneously twice weekly. Etanercept may increase the risk of infection after surgery, lymphoma, leukaemia, and skin cancers.

Discontinuation of Rituximab before dental surgery: dental surgery can be scheduled 2–3 weeks after the last dose due to its extended half-life [7].

Monoclonal Antibodies – B-Cell Depleter

Rituximab (MabThera, Riximyo) targets Cluster of Differentiation 20 (CD20) on B-cells, leading to their destruction. It is used to treat follicular lymphoma, diffuse large B-cell non-Hodgkin lymphoma, chronic lymphocytic leukaemia, and granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris. It is typically administered as 1000 mg intravenously, in two infusions two weeks apart, repeated every 6 months [1,2].

Discontinuation of Rituximab before dental surgery: it is advised dental surgery to be planned 4–6 weeks after infusion, ideally before the next infusion [3].

Monoclonal Antibodies – Interleukin Inhibitors

These inhibitors block specific interleukins (cytokines) involved in immune response and inflammation.

Inhibitors of Interleukin-1 (IL-1)

Anakinra (Kineret)

Anakinra is an IL-1 antagonist used to treat rheumatoid arthritis (RA), Coronavirus Disease 2019, periodic fever syndromes, and cryopyrin-associated periodic syndromes, including Still's disease and familial Mediterranean fever. The usual administration is 100 mg subcutaneously once daily.

Has a half-life of 4–6 hours. It may increase lymphoma risk in patients with rheumatoid arthritis. Side effects include neutropenia, thrombocytopenia, liver issues, and non-infectious hepatitis.

Discontinuation of Rituximab before dental surgery: given its short half-life, dental surgery is safe 1–2 days after the last dose [5].

Sarilumab (Kevzara) targets the IL-6 receptor, used to treat rheumatoid arthritis. Has an elimination half-life of 8–10 days. The usual dosage is 200 mg subcutaneously every 2 weeks.

Recommended discontinuation before dental surgery: it is recommended to wait 2 weeks after the last Sarilumab injection before performing dental surgery [8].

Tocilizumab (RoActemra) is a medication that prevents interleukin-6 from binding to its receptors, reducing inflammation in rheumatoid arthritis, systemic sclerosis, giant cell arteritis, juvenile idiopathic arthritis and polyarthritis. Tocilizumab has an elimination half-life of 13 days (subcutaneous), and 8–14 days (intravenous) and is administered every 1–4 weeks.

Dental surgery and extraction timing: 2 to 4 weeks after the last dose of Tocilizumab [4,5].

Inhibitors of Interleukin-17A

Secukinumab (Cosentyx) is a monoclonal antibody that binds to interleukin-17A, reducing immune activity and disease symptoms in psoriasis, psoriatic arthritis, and ankylosing spondylitis. The half-life of Secukinumab is 27 days (22–31 days). The dosage is 150–300 mg s.c. every 4 weeks [9].

Common side effects include upper respiratory infections (nasopharyngitis, rhinitis).

Recommended discontinuation before dental surgery: due to Secukinumab's half-life and dosing frequency, it is recommended to wait 4–6 weeks after the last injection before dental surgery [9].

Ixekizumab (Taltz)

Ixekizumab (Taltz) inhibits interleukin-17A and is used to treat plaque psoriasis, psoriatic arthritis, and ankylosing spondylitis. It suppresses the immune system with common infections such as upper respiratory tract infections, oral candidiasis, conjunctivitis, and tinea. The half-life of Ixekizumab is 13 days (11–17 days). Dosage: 80 mg every 4 weeks [10].

Recommended discontinuation before dental surgery: dental surgery should be done between the 4th and 6th week post-injection for reduced infection risk and better healing.

Inhibitors of IL-12 and IL-23

Ustekinumab (Stelara)

Ustekinumab (Stelara) is a human immunoglobulin G subclass (IgG)1κ monoclonal antibody targeting interleukin-12/23, indicated for the treatment of psoriasis, psoriatic arthritis, ulcerative colitis, Crohn's disease [5].

Inhibitors of IL-23

Risankizumab (Skyrizi) is a humanized IgG1 monoclonal antibody inhibiting IL-23-dependent cellular signaling and pro-inflammatory cytokine release. It is indicated for the treatment of plaque psoriasis, active psoriatic arthritis, Crohn's disease, and ulcerative colitis. Its half-life is approximately 28 days (21 to 30 days). The dosage in psoriasis is 150 mg every 12 weeks, and in Crohn's Disease: 360 mg subcutaneously every 8 weeks [1].

Recommended discontinuation before dental surgery: dental surgery is ideally scheduled around 4–6 weeks after the last injection [1].

Guselkumab (Tremfya) is a human IgG1λ monoclonal antibody targeting interleukin-23, indicated for the treatment of plaque psoriasis, and psoriatic arthritis.

Elimination half-life of Guselkumab is approximately 15–19 days. The dosage for psoriasis and psoriatic Arthritis is 100 mg every 8 weeks [7].

Recommended discontinuation before dental surgery: surgery/extraction is generally advised between the 4th and 6th week following the last injection of Guselkumab [7].

Monoclonal Antibodies – Janus Kinase (JAK) Inhibitors

Baricitinib (Olumiant) is a JAK inhibitor that targets JAK1 and JAK2, reducing JAK-mediated inflammation in rheumatoid arthritis, atopic dermatitis, and severe Coronavirus Disease 2019 (COVID-19). Its half-life is approximately 12–18 hours with a dosage for rheumatoid arthritis and atopic dermatitis 2–4 mg once daily. For severe COVID-19: 4 mg once daily for up to 14 days [11,13].

Recommended discontinuation before dental surgery: dental extraction/surgery can be considered 1–2 days after discontinuing Baricitinib [14].

Tofacitinib (Xeljanz) is an oral Janus kinase inhibitor used to treat rheumatoid arthritis, ulcerative colitis, and atopic dermatitis. It has a half-life–6 hours, depending on patient factors and dosage. The dosage in rheumatoid arthritis and atopic dermatitis is 5–10 mg twice daily [13]

Recommended discontinuation before dental surgery: due to its short half-life, a break of only 1–2 days before extraction is generally sufficient [15].

Filgotinib (Jyseleca), an oral JAK inhibitor, is primarily used for rheumatoid. Filgotinib's half-life is around 5–9 hours. The dosage in rheumatoid arthritis is 100 mg once daily.

Recommended discontinuation before dental surgery: extraction can typically proceed 1–2 days after the last dose due to its short half-life [11,13].

Upadacitinib (Rinvoq) is an oral JAK inhibitor, indicated for rheumatoid arthritis and atopic dermatitis.

Elimination of a half-life is approximately 6–10 hours. The dosage is 15 mg once daily.

Recommended discontinuation before dental surgery: due to its short half-life, surgery is generally safe 1–2 days post-dosing [11,13].

Monoclonal Antibodies – Anti-Epidermal Growth Factor Receptor (EGFR) Monoclonal Antibodies

Trastuzumab (Herceptin) targets Human Epidermal Growth Factor Receptor 2 (HER2) receptors, primarily treating HER2-positive breast and gastric cancers by slowing tumor growth. Depending on the indication dosage is 4–6 mg/kg every three weeks.

Recommended discontinuation before dental surgery: although Trastuzumab does not suppress immunity like TNF inhibitors; caution is advised for surgical procedures [11].

Cetuximab (Erbitux) is an anti-EGFR monoclonal antibody used for head, neck, and colorectal cancers, targeting cancer cells with high EGFR expression. Cetuximab has a half-life of approximately 5 days.

Recommended discontinuation before dental surgery is at least 4–6 weeks [1,2].

Monoclonal Antibodies - Anti-Coagulant And Anti Neo–Vascularisation Agents

Abciximab, the fragment, antigen-binding section of the chimeric human-murine monoclonal antibody 7E3 binds to the platelet receptor glycoprotein IIb/IIIa and is used as an antiplatelet agent. The main adverse effects are bleeding and thrombocytopenia [11].

Bevacizumab (Avastin), a vascular endothelial growth factor (VEGF) inhibitor, blocks angiogenesis is used in anticancer chemotherapy and for the treatment of age-related macular degeneration [11].

Monoclonal Antibodies - Receptor Activator of Nuclear Factor-Kappa B Ligand Blockers

Denosumab is a human monoclonal antibody that targets the receptor activator of nuclear factor κB ligand (RANKL) and blocks it, inhibiting osteoclast growth and action – resulting in reduced bone resorption and increasing bone density. Denosumab is used to prevent osteoporosis but severe adverse events include skin exanthemas and infections, decreased physiological bone turnover and jaw osteonecrosis [11].

Monoclonal Antibodies – Other Antibodies

Vedolizumab (Entyvio) is a recombinant humanized IgG1 monoclonal antibody that inhibits leukocyte migration to the intestines. It is indicated for the treatment of ulcerative colitis and Crohn's disease [1,2].

Fusion Proteins (Soluble Cytokine Receptors or Ligands)

Abatacept (Orencia): a Cytotoxic T-Lymphocyte Antigen-4 Immunoglobulin (CTLA-4) immunoglobulin fused protein that inhibits T-cell activation. It is indicated for the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, and systemic lupus erythematosus. Has an elimination half-life of 13–16 days.

The recommended dose for rheumatoid arthritis is 750 mg every 4 weeks.

Recommended discontinuation before dental surgery: dental surgery may be considered 3–4 weeks after the last Abatacept dose [1,4].

Alefacept (Amevive): an immunoglobulin G1 fused protein targeting CD2 on T cells for psoriasis treatment. It has an elimination half-life 12–15 days. For plaque psoriasis dose is 15 mg s.c. once weekly for 12 weeks, followed by 30 mg once every 2 weeks.

Recommended discontinuation before dental surgery: dental surgery may be considered 3–4 weeks after the last Alefacept dose [1,16].

Erythropoietin (Epogen). The active ingredient epoetin alfa (Alfa Hexal) mimics natural erythropoietin to stimulate red blood cell production in the bone marrow. It is indicated in anaemia caused by chemotherapy, chronic kidney disease, and other conditions. Erythropoietin's half-life is 4–13 hours. In anaemia in chronic kidney disease initial dose is 50–150 units/kg body weight once to three times weekly [1].

Recommended discontinuation before dental surgery: it is generally safe to consider dental surgery 1–2 days after the last dose of erythropoietin [16].

Denileukin Diftitox (Ontak) is a genetically engineered cytotoxic fusion protein that includes the amino acid sequence for the enzymatically active part of diphtheria toxin fused with human interleukin-2, creating a molecule cytotoxic to cells with the target IL-2 receptor. It is indicated for the treatment of cutaneous T-cell lymphoma whose malignant cells express the CD25 component of the IL-2 receptor. Its half-life is 70 to 80 minutes, but effects on the immune system may persist longer.

Recommended discontinuation before dental surgery: it is generally advisable to wait 2–4 weeks after discontinuation of treatment [1].

Immunomodulators Blocking Phosphodiesterase 4 Activity

Apremilast (Otezla) blocks phosphodiesterase 4 activities, reducing inflammatory cytokine levels and symptoms in psoriasis, psoriatic arthritis, and Behçet's disease. Unlike JAK inhibitors and biologics, it suppresses inflammatory processes without fully suppressing the immune system. Apremilast's elimination half-life is 6–9 hours. In plaque psoriasis dose is 30 mg once daily.

Recommended discontinuation before dental surgery: dental surgery can be considered 1–2 days after the last dose [17].

Impact of Biological Therapy on Oral Health. Recommendations for Dental Surgical Treatment

The use of biological drugs, despite their considerable therapeutic benefits, may give rise to various dental and oral complications. These medications modulate specific components of the immune response, thereby increasing the risk of immunosuppression. As a result, latent infections such as hepatitis B, hepatitis C, and tuberculosis may reactivate. It is important to note that there is currently no specific guidance tailored to dental or oral surgical procedures. The subsequent discussion will address, in detail, the most prevalent oral complications associated with these therapies, as well as the recommended practices to be followed prior to dental surgery [2,4,16].

Reactivation of Latent Infections

Tuberculosis may present clinically with redness and irritation in the back of the throat, due to chronic cough, along with a solitary, painful ulcer on the tongue. This lesion, characterized by irregular borders, raised edges, and exudate, is sometimes mistaken for a malignant lesion [16].

In a study by Maeda T *et al.* [18] involving 3024 patients tested for tuberculosis, 42 tested positive. They reviewed 19 guidelines/consensus statements by 13 organizations relevant to tuberculosis screening among patients treated with biologic medications of which 12 had specific recommendations for TB screening.

Ernst D *et al.* [19] report a case of reactivation of *Mycobacterium tuberculosis* in a 70-year-old woman, treated with TNF inhibitors for rheumatoid arthritis for five years. She was admitted with oral ulcers in the left maxilla. Biopsies revealed a necrotizing granulomatous inflammatory reaction, later confirmed as a *Mycobacterium bovis* infection [19].

Additionally, viral, bacterial, or fungal opportunistic infections can develop, particularly with concurrent use of other immunosuppressants, such as corticosteroids or methotrexate [2–4].

A study by Tudesq JJ *et al.* [20] of 101 rituximab-treated patients found 228 infectious events in 74 patients (73.3%) over a median follow-up of 30.4 months. Infections occurred ~3.1 months after the last of five infusions. Severe infections were more frequent in monoclonal hematologic disease (MHD) (58.0%) than autoimmune disease (AID) (28.1%, $p < 0.001$). Opportunistic pathogens appeared in 7.8% of AID and 11.0% of MHD cases ($p = 0.49$). Fatalities were higher in MHD (13.0%) versus AID (4.7%, $p = 0.044$). Ten patients (9.9%) experienced life-threatening, polymicrobial, and opportunistic infections, leading to death in seven cases [20].

Fungal Infections and Oral Manifestations

Though oral candidiasis, cryptococcosis, histoplasmosis, blastomycosis, and aspergillosis are not frequently seen as opportunistic infections with biological treatment, clinicians should be aware of potential oral manifestations and differentiate these from malignant processes.

Oral candidiasis may present as:

Pseudomembranous candidiasis: thick, white, plaque-like membrane that reveals erythematous tissue upon removal.

Erythematous atrophic candidiasis: bright red, primarily affecting the tongue, and accompanied by a burning sensation. The image presents the author's own research. In accordance with ethical guidelines, the patient's informed consent was obtained for the use of these images (Fig. 1).

Hyperplastic candidiasis (candida leukoplakia): located on the lateral tongue and buccal mucosa.

Candidiasis can enter the bloodstream, leading to deep mycotic infections resistant to treatment and causing potential coagulation issues [21].

Research by Vila T *et al.* [21] highlights the roles of cytokines IL-17 and TNF-α in controlling Candida infections. Conti HR and Gaffen SL [22] also emphasize the crucial role of TNF-α and IL-17A in mediating immune responses to *Candida albicans*, suggesting a dual role of these cytokines in infection control and inflammation.

Cryptococcal infections affect the gums, palate, or recent extraction sites, presenting as nodules of granulation tissue, indurated ulcers, and swelling. Fig. 2 presents an image of the author's own patient. In accordance with ethical guidelines, the patient's informed consent was obtained for the use of the image (Fig. 2).

Blastomycosis may appear as ulcerative lesions and can lead to bone necrosis. Histoplasmosis results in pseudomembranous ulcers and lesions on the tongue, buccal mucosa, gums, or lips. Aspergillus infections cause painful necrotic lesions on the gums, palate, or back of the tongue, appearing yellow, grey, or black with ulcerated bases [4].

Reactivation of Herpesviridae can lead to:

Labial herpes: small, painful, fluid-filled vesicles that can merge into one large blister and localize on the lip borders, tongue, palate, or buccal mucosa.

Gingivostomatitis, which may develop with herpes types 1 and 2, causes mucosal ulcers, erythematous tissues, or acute gingivitis.

Varicella zoster can affect the facial nerve (N. facialis), causing unilateral facial paresis or paralysis.

Oral hairy leukoplakia often appears on the lateral tongue edges and buccal commissures.

Cytomegalovirus presents as medium-sized ulcers on the palate and infections of the salivary glands.

Mononucleosis infection can be identified by palatal petechiae, tonsillitis, and cervical lymphadenopathy.

Kaposi's sarcoma manifests as raised purple lesions on the skin or oral mucosa [4].

With TNF-α inhibitors, lichen-like lesions may develop, along with erythema multiforme, which presents as diffuse redness, irregular oral ulcers, crusting, and lip bleeding. For patients on calcineurin inhibitors, fibrous polyps may develop, occasionally large and lobulated, on the lateral parts of the tongue, lip, or buccal mucosa [4].

Due to existing immunosuppression, normal inflammatory processes may be inhibited, increasing the risk of bleeding, delayed wound healing, and infection development during dental surgery, which requires specific perioperative management [1–3]:

Preoperative evaluation of liver function;

Blood counts and coagulation status;

Potential temporary discontinuation of biologic therapy;

Postoperative monitoring of the healing process [1–3].

Liver Damage Associated with Biologic Medications

Liver damage caused by biological medications can affect dental surgical procedures by increasing the risk of bleeding (due to impaired clotting factor production), delaying healing, and altering drug metabolism, which may lead to potential toxicity. Additionally, it heightens the risk of infection and complicates anaesthesia management. Preoperative evaluation and careful drug selection are essential to minimize these complications.

TNF-α, IL-6 inhibitors, and anti-CD20 monoclonal antibodies can affect the liver through:

Immune-mediated damage: biological drugs may trigger autoimmune hepatitis or other liver inflammation.

Hepatotoxicity: biologics can directly affect liver cells, sometimes leading to drug-induced hepatitis or other liver injuries.

Elevated liver enzymes: temporary Alanine Aminotransferase (ALT)/Aspartate Aminotransferase (AST) increases may indicate reversible liver damage.

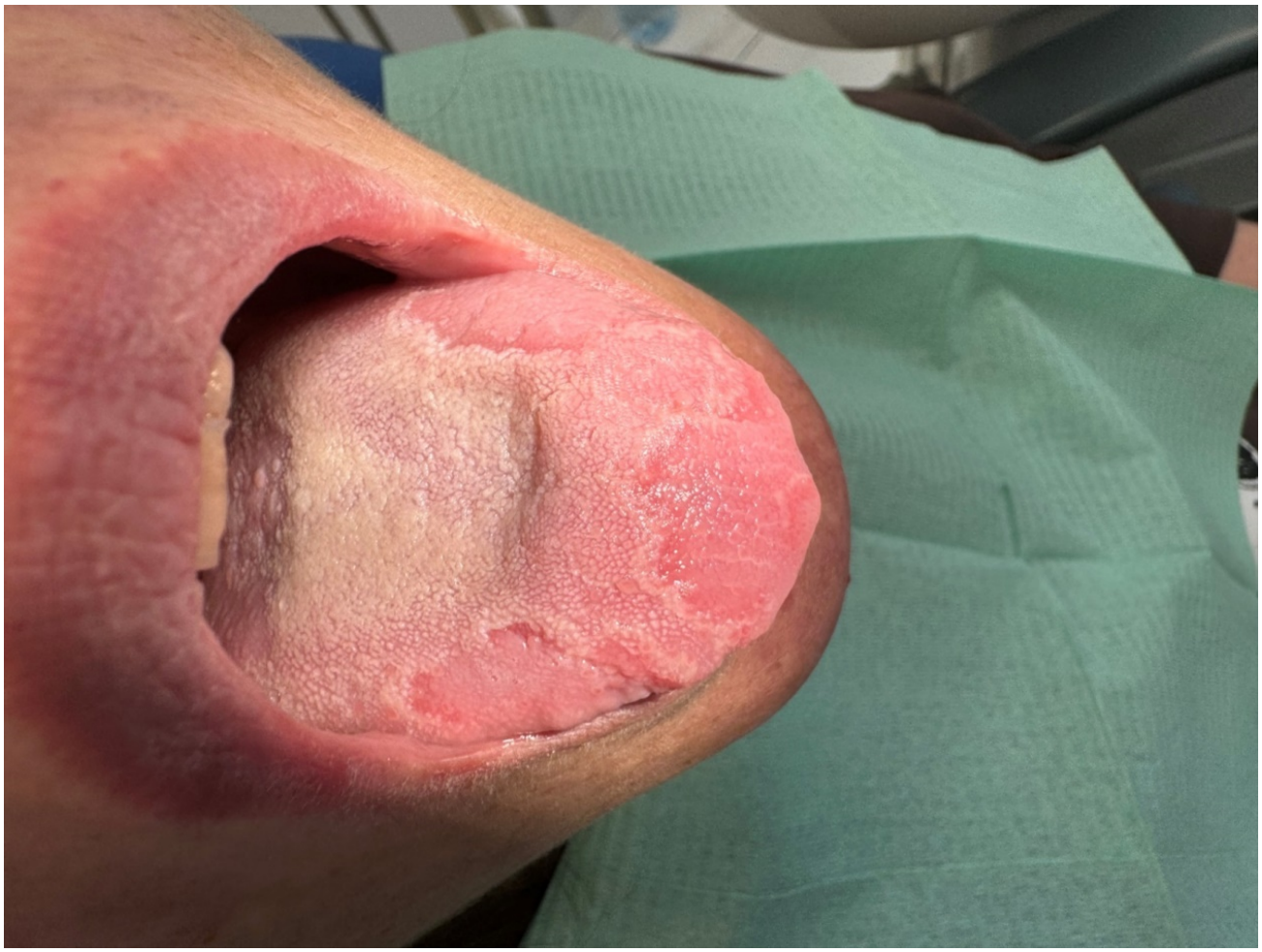

Fig. 1. Erythematous atrophic candidiasis on the tongue.

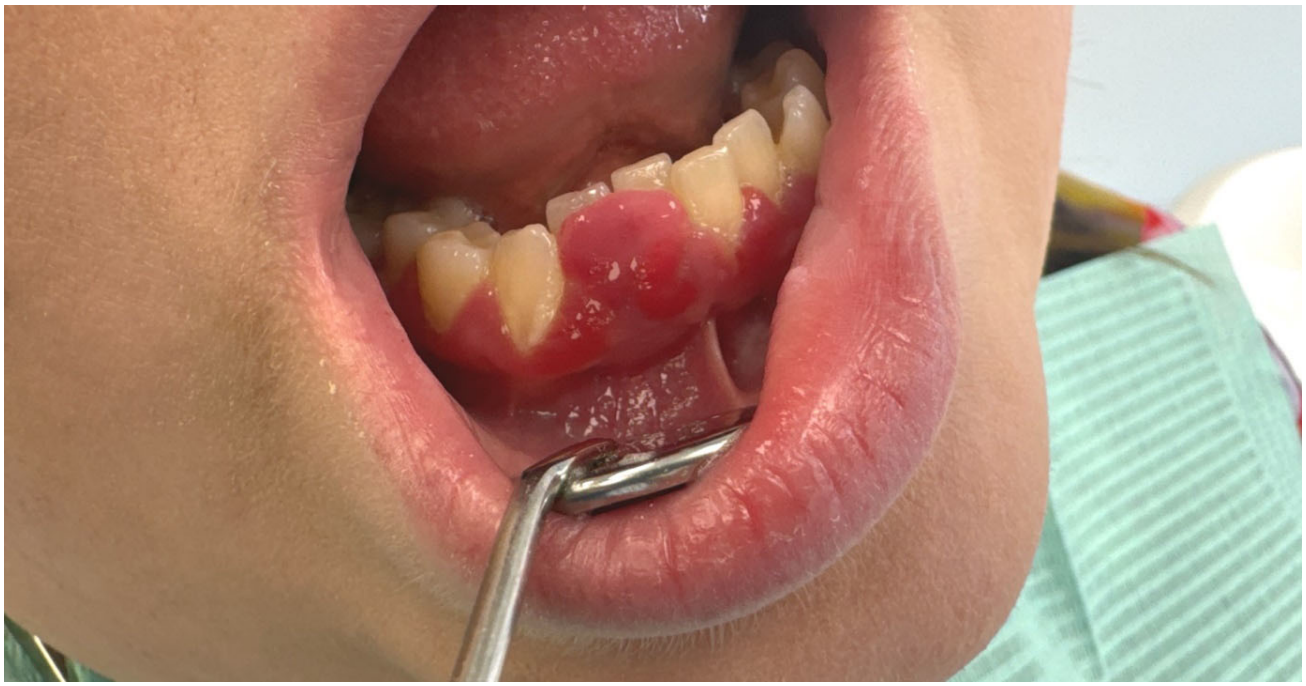

Fig. 2. Gingival cryptococcal infection.

Reactivation of latent infections: immunosuppressive biologics may reactivate chronic viral infections like hepatitis B or C, leading to acute hepatitis or cirrhosis.

Liver steatosis: some TNF and Interleukin inhibitors are linked to liver steatosis, potentially leading to non-alcoholic steatohepatitis (NASH) and cirrhosis [23].

Immune checkpoint inhibitors (ipilimumab), used in cancer treatment, can induce severe autoimmune hepatitis [23].

Prevention and Monitoring:

For patients prescribed biological drugs, regular monitoring of lipid levels, liver enzyme tests, prothrombin time (PT), and the international normalized ratio (INR) are crucial [23].

Increased Risk of Hematological Disorders

Haematological disorders caused by biological therapy can increase the risk of bleeding, delay healing, and complicate oral surgical procedures [11]. The most common haematological disorders include:

Bone Marrow Suppression

Immunomodulators can lead to myelosuppression, resulting in: anaemia, leukopenia with increasing infection risk and thrombocytopenia heightening bleeding risk [24].

Immune-Mediated Hematological Disorders

Biological drugs may activate autoimmune processes, leading to:

Autoimmune haemolytic anaemia: where the immune system attacks red blood cells.

Immune thrombocytopenic purpura (ITP): where the immune system attacks platelets, causing a low platelet count and an increased risk of bleeding [24].

Lymphoproliferative Disorders

Long-term use of biological agents can increase the risk of hematological malignancies like lymphoma, particularly with TNF inhibitors (e.g., infliximab, adalimumab, etanercept) in autoimmune conditions such as rheumatoid arthritis. While the risk remains low, B-cell inhibitors (e.g., rituximab) may cause lymphoproliferative disorders, especially in patients with latent Epstein-Barr virus [24].

Reactivation of Latent Viral Infections

Some biological drugs may suppress immune responses and reactivate latent viruses (Epstein-Barr virus, cytomegalovirus), leading to haematological diseases such as virus-associated lymphomas [24].

Hematologic Side Effects from Immune Checkpoint Inhibitors

Immune checkpoint inhibitors (nivolumab, ipilimumab) may provoke severe autoimmune reactions such as pancytopenia or aplastic anaemia [24].

Biological drugs often associated with hematologic complications are:

TNF Inhibitors like infliximab, adalimumab, and etanercept are associated with an increased risk of non-Hodgkin lymphoma. They may also cause anaemia, thrombocytopenia, and leukopenia [24–26].

Rituximab is a CD20-targeting agent used for lymphoma and autoimmune diseases and is linked to secondary lymphomas and other lymphoproliferative disorders [24].

Immune checkpoint inhibitors such as Ipilimumab and nivolumab can cause severe pancytopenia and aplastic anaemia [24].

Monitoring complete blood count, platelet count and function, as well as prothrombin time, INR and bleeding time, is essential before any dental surgery in patients on biological therapy due to an increased risk of haematological disorders, including thrombocytopenia and risk of liver disease [16,24].

Haemostasis Abnormalities

An increased risk of bleeding may arise due to:

Impact on platelets and coagulation: TNF inhibitors may impair normal platelet function. Rituximab may affect coagulation factors, while tocilizumab may influence fibrinogen levels [27]. Üsküdar Cansu D *et al.* [27] reported a case of hypofibrinogenemia with tocilizumab use.

Effects on blood vessels: TNF-α inhibition leads to vascular dysfunction, while anti-interleukin agents, such as guselkumab, may impact endothelial cells, altering vascular permeability. Falsetti L *et al.* [25] reported a case of adalimumab-induced thrombocytopenic microangiopathy.

Hematological disorders: Immune checkpoint inhibitors for cancer, can cause myelosuppression, leading to aplastic anemia, leukopenia, pancytopenia, or thrombocytopenia. Autoimmune hemolytic anaemia and immune thrombocytopenic purpura may also occur [23]. Boegeholz J *et al.* [28] reported 34 cases of neutropenia that developed a mean of 10.5 weeks after the first administration of immune checkpoint inhibitors. Paul C *et al.* [29] reported reactivation of Epstein-Barr and cytomegalovirus, with virus-associated lymphomas developing. Rajakulendran *et al.* [30] reported a 14.3% incidence of neutropenia in patients treated with anti-TNF drugs, associated with suppression of stem cell differentiation and bone marrow hypoplasia.

Preoperative assessment of hemostasis/hematological abnormalities:

- Absolute neutrophil count (ANC);
- Absolute lymphocyte count (ALC);
- Hemoglobin (Hb) and Hematocrit (HCT);
- Evaluation of platelets (number and morphology, function);
- Prothrombin time;
- Activated partial thromboplastin time (APTT);
- Fibrinogen [2,17,23].

Table 2. Half-life, dosing intervals, and surgery schedule times.

Drug	Half-life	Dosing interval	Timing for surgery relative to last biologic dose
1. Interferons			
Interferon-alfa	2–8 hours	50 mg subcutaneously 1 or 2 times a week	2 to 4 weeks after stopping therapy
Interferon-beta	8–12 hours	Monthly i.v. Weekly s.c.	
Interferon-gamma	4–10 hours	30 mg once every 2 weeks	
2. Antibodies			
2.1. TNF-α antagonists			
Adalimumab (Humira)	12–14 days	Every 2 weeks	1 to 2 weeks after the last intake
Certolizumab (Cimzia)	11–14 days	Every 2 weeks	1 to 2 weeks after the last intake
Golimumab (Simponi)	12–14 days	Every 4 weeks	1 to 2 weeks after the last intake
Infliximab (Remicade)	8–10 days	Every 4, 6 or 8 weeks	2 to 4 weeks after the last intake
Etanercept (Enbrel)	70 hours (range 7 to 300 hours)	50 mg subcutaneously Weekly or twice weekly	2 to 3 weeks after the last intake
2.2. B-cell depletor			
Rituximab (Mabthera)	18–32 days	Two intakes 2 weeks apart, no more frequent than every 6 months	4 to 6 weeks after a rituximab infusion, ideally before the next infusion
2.3. Interleukin inhibitors			
Anakinra (Kineret)	4–6 hours	100 mg s.c. once a day	1–2 days after the last intake
Sarilumab (Kevzara)	8–10 days	200 mg s.c. Every 2 weeks	2 weeks after the last intake /skipping a dose/
Tocilizumab (Roactemra) i.v.	11–13 days	Every 4 weeks	2 to 4 weeks after the last intake
Tocilizumab (Roactemra) s.c.	11–13 days	Every 1 to 4 weeks	2 to 4 weeks after the last intake
Secukinumab (Cosentyx)	27 days	150–300 mg s.c. Monthly	4 to 6 weeks after the last intake
Ixekizumab (Taltz)	11–17 days	Monthly s.c.	4 to 6 weeks after the last intake
Ustekinumab (Stelara)	15–32 days	Every 12 weeks	4 to 6 weeks after the last intake
Risankizumab (Skyrizi)	21–30 days	Every 8 to 12 weeks s.c.	4 to 6 weeks after the last intake
Guselkumab (Tremfya)	15–19 days	Every 4–8 weeks s.c.	4 to 6 weeks after the last intake
2.4. Janus kinase inhibitors			
Baracitinib (Olumiant)	12–18 hours	Daily oral intake	Stop dosing 2 days prior to surgery
Tofacitinib (Xeljanz)	3–6 hours	Twice daily oral intake	
Filgotinib (Jyseleca)	5–9 hours	Daily oral intake	
Upadacitinib (Rinvoq)	6–10 hours	Daily oral intake	

Table 2. Continued.

Drug	Half-life	Dosing interval	Timing for surgery relative to last biologic dose
2.5. Anti-epidermal growth factor receptors			
Trastuzumab (Herceptin)	28–30 days	6–8 mg/kg each 3 weeks	do not suppress the immune system like TNF inhibitors, but caution is advised in surgical procedures
Cetuximab (Erbitux)	70–80 hours	Once a week	3 to 4 weeks after the last intake
2.6. Monoclonal antibodies–anti-coagulant and anti-neo-vascularisation agents			
Abciximab (ReoPro)	30 minutes–2 hours	0.25 mg/kg i.v. before percutaneous coronary intervention procedure. Maintenance dose: 0.125 mcg/kg/min is given for 12 hours post-procedure.	24 to 48 hours following administration
Bevacizumab (Avastin)	20 days	5–10 mg/kg every 2–3 weeks	4 to 6 weeks after the last bevacizumab dose
2.7. Monoclonal antibodies–receptor activator of nuclear factor-kappa b ligand blockers			
Denosumab (Prolia)	26–48 days	60–120 mg s.c. every 4–6 months.	3 to 6 months after the last dose of denosumab
2.8. Other antibodies			
Vedolizumab (Entyvio)	25 days	300 mg single-dose vial i.v. every 2 to 8 weeks 108 mg/0.68 mL prefilled syringe/pen s.c. every 2 weeks	3 to 4 weeks after the last 12 weeks after the last intake
3. Fusion proteins			
Abatacept (Orencia) i.v	13–16 days	Monthly i.v.	Week 5 after the last intake
Abatacept (Orencia) s.c.		Weekly s.c.	Week 2 after the last intake
Alefacept (Amevive)	12–15 days	30 mg once each 2 weeks.	3 to 4 weeks after the last intake
Erythropoietin (Epogen)	4–13 hours	Once every 1 to 3 weeks	1 to 2 days after the last intake
Denileukin diftitox (Ontak)	70–80 min.	Once or twice weekly	2 to 4 weeks after the last intake
4. Immunomodulators blocking the action of phosphodiesterase			
Apremilast (Otezla)	6–9 hours	Daily oral intake	Stop dosing 2 days prior to surgery

i.v., intravenous; s.c., subcutaneous.

Additional tests:

- Coagulopathy tests;
- D-dimer tests;
- Liver transaminases;
- Lipid indicators [2,16].

Management of Infection Risk

The approach to biological therapy in preparation for upcoming dental surgery should be individualized in consultation with the treating physician. Factors to consider include the type of underlying disease, risk of disease flare-up, comorbidities, ongoing immunosuppressive therapy, and the nature of the surgery.

Planned procedures may be scheduled at the end of the dosing interval, when the immunosuppressive effect of the drug is at its lowest. Alternatively, therapy may be paused for a period of 3–5 half-lives of the drug before surgery (Table 2, Ref. [1,7–10,12,14,15,17]).

Antibiotic Prophylaxis before Dental Surgery for Patients on Biological Therapy

Antibiotic prophylaxis before dental surgery is not routinely prescribed for patients on biological therapy. However, it may be indicated in the following cases:

Increased Risk of Infection

- Long-term or aggressive biological therapy leading to significant immunosuppression.

- Additional risk factors, such as heart disease, chronic conditions, or prior surgeries with implants (joint prostheses).

- Severe periodontal infections/active inflammation requiring surgical intervention [2,12,16].

Invasive dental procedures: procedures with high bacteraemia risk, such as multiple/surgical extractions, implant placements, deep periodontal procedures, or abscess surgery [2,12,16].

Prevention of infections leading to osteonecrosis of the jaws (ONJ): patients receiving biological therapies, such as denosumab, bisphosphonates, or immune-modulating agents (e.g., TNF inhibitors), are at increased risk of developing ONJ, especially following invasive dental procedures. To minimize this risk, prophylactic antibiotics should be initiated 1 hour prior to the procedure and continued for a short post-operative period, typically 3–5 days [31–33].

Concurrent use of other immunosuppressants: if the patient is also taking other immunosuppressive medications (corticosteroids or methotrexate), infection risk further increases, making antibiotic prophylaxis advisable.

Previous infections after surgical procedures: patients who have had infections following previous dental or surgical interventions.

Osteonecrosis of the Jaws

Osteonecrosis of the jaws is a serious complication that has been associated with biological therapies, such as denosumab, bevacizumab, or immune-modulating agents (e.g., TNF inhibitors) [31–34].

Denosumab is a monoclonal antibody that inhibits osteoclast activity, reducing bone resorption. While effective in treating osteoporosis and preventing skeletal-related events in cancer patients, denosumab has been linked to cases of ONJ. O'Halloran M *et al.* [31] reported two cases of ONJ. The first patient developed oral osteonecrosis six months after starting denosumab treatment. The second patient developed an oroantral fistula six months after receiving denosumab injections. The U.S. Food and Drug Administration (FDA) notes that denosumab can cause serious adverse effects, including ONJ, hypocalcemia, serious infections, and dermatologic reactions [32]. Pedro Diz *et al.* [34] report a case of denosumab-related osteonecrosis of the jaw in a patient with prostate cancer, following a molar extraction six months after stopping denosumab therapy.

Bevacizumab, an anti-angiogenic drug targeting vascular endothelial growth factor, is used in cancer therapy to inhibit tumor blood vessel formation. However, it has been associated with ONJ, particularly when combined with bisphosphonates. Studies have reported cases of bevacizumab-induced ONJ, especially in patients receiving both bevacizumab and bisphosphonates [34]. Santos-Silva AR *et al.* [35] reported a case of a 61-year-old man who developed mandible osteonecrosis during treatment with bevacizumab, suggesting a potential link between bevacizumab's anti-angiogenic properties and osteonecrosis of the jaw.

Risk factors for developing ONJ while on these medications include invasive dental procedures, poor oral hygiene, use of corticosteroids, and underlying health conditions such as cancer or osteoporosis. Preventive measures include maintaining excellent oral hygiene, regular dental check-ups, and avoiding invasive dental procedures during treatment with these drugs. If dental surgery is necessary, drug cessation may be considered, although the benefits of this approach are still under investigation.

Management of ONJ involves conservative treatments such as antimicrobial mouth rinses, antibiotics, and pain management. In severe cases, surgical intervention may be required. Early detection and a multidisciplinary approach are crucial for effective management [31–35].

Resuming Biological Therapy after Surgery

Resuming biological therapy post-surgery should occur when wound healing is satisfactory, sutures have been removed, and there are no clinical signs of infection, typically confirmed at a follow-up visit about 14 days post-surgery.

In emergency surgery, it may not be possible to plan or pause therapy, so these patients should be closely monitored for signs of infection or other postoperative complications [2,12,16].

Conclusion

Biological therapies have transformed the treatment of chronic inflammatory and autoimmune conditions, showing significant effectiveness in diseases like rheumatoid arthritis, psoriasis, inflammatory bowel disease, and cancer. However, these therapies require caution in oral surgery due to their effect on the immune system, delayed healing, and higher infection risk. Studies show that biological agents can affect immune function, making recovery after surgery more difficult.

For the most appropriate treatment such patients require a multidisciplinary approach involving oral surgeons, rheumatologists, and other healthcare providers. Key recommendations for safe practice include a thorough preoperative assessment, individualized risk stratification, and careful monitoring throughout the perioperative period. Temporarily cessation of biological agents, when feasible, has been proposed as a strategy to reduce complications, but decisions should carefully balance the risk of disease recurrence against the need for surgical safety. Clinical guidelines suggest evaluating the timing and need for discontinuing biologics to reduce risks while effectively managing flare-ups.

In addition, strong infection control practices and proper postoperative care are crucial for reducing complications, such as infections and delayed healing. Further research is required to refine clinical protocols and improve patient outcomes, particularly as biologic therapies continue to advance.

Availability of Data and Materials

Not applicable.

Author Contributions

AD made substantial contributions to the conception and design of the manuscript, wrote the first draft, and performed the analysis and interpretation of the data. PP contributed to the acquisition of data, assisted with subsequent revisions of the manuscript, and provided critical input on the analysis and interpretation of the data. Both authors have reviewed and approved the final version. Both authors contributed significantly to editorial changes of important content. Both authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Informed consent was obtained from the patients for the images presented in Figs. 1,2.

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Conflict of Interest

The authors declare no conflict of interest.

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