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Immunosuppressive Therapy in Dental Medicine: Clinical Applications and Adverse Effects

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ABSTRACT

This master's thesis provides a comprehensive analysis of immunosuppressive therapies in the context of dental medicine. The thesis systematically reviews the historical progression, classifications, and molecular mechanisms of key immunosuppressive drugs, including corticosteroids, calcineurin inhibitors, nucleotide biosynthesis inhibitors, and biological agents. Focusing on their pharmacodynamics and pharmacokinetics, the research explains how these drugs modulate various aspects of the immune response, such as suppressing progenitor cell formation, inhibiting lymphocyte and monocyte proliferation and differentiation, and disrupting nucleic acid and protein biosynthesis.

Additionally, the thesis explores the clinical implications of these therapies in dental practices, highlighting both therapeutic benefits and potential adverse effects on oral health.

Methodologies include a detailed literature review and analysis of clinical data to provide a robust framework for understanding these therapies.

Through a synthesis of literature and clinical data, this research aims to contribute to a more nuanced understanding of immunosuppressive therapy management in dental patients, advocating for an interdisciplinary approach to optimize treatment efficacy and patient safety.

ZUSSAMENFASSUNG

Diese Masterarbeit bietet eine umfassende Analyse immunsuppressiver Therapien im Kontext der Zahnmedizin. Die Arbeit untersucht systematisch den historischen Verlauf, die Klassifizierungen und die molekularen Mechanismen wichtiger immunsuppressiver Medikamente, darunter Kortikosteroide, Calcineurin-Inhibitoren, Nukleotidbiosynthese-Inhibitoren und biologische Wirkstoffe. Die Forschung konzentriert sich auf ihre Pharmakodynamik und Pharmakokinetik und erklärt, wie diese Medikamente verschiedene Aspekte der Immunantwort modulieren, z. B. die Unterdrückung der Bildung von Vorläuferzellen, die Hemmung der Proliferation und Differenzierung von Lymphozyten und Monozyten und die Störung der Nukleinsäure- und Proteinbiosynthese.

Darüber hinaus untersucht die Arbeit die klinischen Auswirkungen dieser Therapien in der Zahnarztpraxis und hebt sowohl den therapeutischen Nutzen als auch die möglichen negativen Auswirkungen auf die Mundgesundheit hervor.

Zu den Methoden gehören eine detaillierte Literaturübersicht und eine Analyse klinischer Daten, um einen soliden Rahmen zum Verständnis dieser Therapien zu bieten.

Durch eine Synthese aus Literatur und klinischen Daten soll diese Forschung zu einem differenzierteren Verständnis der immunsuppressiven Therapie bei Zahnpatienten beitragen und für einen interdisziplinären Ansatz zur Optimierung der Behandlungswirksamkeit und Patientensicherheit plädieren.

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1. INTRODUCTION

1.1. The basics of immunosuppression

Immunosuppression describes processes and conditions that reduce or inhibit the body's own immune response. It can be unintentional and is often due to the ageing process, poor nutrition, certain diseases such as leukaemia, lymphoma and multiple myeloma, or stress. On the other hand, immunosuppression can also be intentional, which means that the body's own immune response is deliberately suppressed in order to achieve a specific therapeutic or clinical goal. This type of immunosuppression is used in situations where the immune response is excessive or harmful for example in autoimmune diseases, organ transplantation or the treatment of malignant diseases.

The immune response can be suppressed or weakened in various ways, including the administration of antigens, specific antibodies, cytokine antagonists and agonists, cytostatics, antisera, hormones, radiotherapy, surgical removal of lymphatic tissue, and immunosuppressants. [1,2]

There are two types of immunosuppression: non-specific and specific.

Non-specific immunosuppression is an immune response that refers to a general or global suppression of immune system activity without selectively targeting specific antigens or specific cells. This form of immunosuppression effects a broader range of immune functions and reduces the body's overall ability to recognise and respond to a variety of antigens, including external pathogens and its own tissues.

Although non-specific immunosuppression is useful in certain situations, such as organ transplants or the treatment of autoimmune diseases, it can increase the risk of infections and other complications due to the overall suppression of the immune system. It is therefore crutial to carefully weigh up the benefits and risks of this therapy before using it.

Specific immunosuppression is the selective suppression of the immune system's activity against certain antigens without impairing immune function in general. This means that the immunosuppressive effect is directed at specific target molecules or cells, reducing the immune

response to these specific targets without impairing the function of the rest of the immune system. [2,3]

Nevertheless, it is necessary to monitor and manage the risks of specific immunosuppressive therapies in order to avoid complications such as infections, tumours, metabolic disorders, arterial hypertension, and other side effects.

1.2. History of immunosuppressant development

Immunosuppressive therapy is a central aspect of modern medicine, specifically in the context of organ transplantation and the treatment of autoimmune diseases. Its development spans several phases, from early research to modern approaches that target specific parts of the immune system.

The first stage of development began in the late 1950s and early 1960s involving the use of cytostatic drugs and antimetabolites to control the immune response. Cytostatic or cytotoxic agents such as alkylating agents like cyclophosphamide, purine analogs like 6-mercaptopurine and azathioprine, folate analogs like methotrexate, and pyrimidine analogs like cytosine arabinoside have been useful in regulating the immune response. These drugs act at different levels of the immune response, for example by suppressing the formation of progenitor cells, destroying or blocking immunocompetent cells, suppressing the proliferation and differentiation of lymphocytes and monocytes, inhibiting the biosynthesis of nucleic acids and proteins.

However, the use of these non-specific drugs, whose effect is not limited to immunocompetent cells, harbors certain dangers. These drugs caused uncontrolled damage to all cells in the process of mitosis, including normal, functional cells that are necessary for the survival of the organism.

The second phase in the development of immunosuppressive therapy, which spanned the 1960s and 1970s, involved the combination of various agents with the aim of achieving maximum suppression of the immune response with minimal side effects. [6] Corticosteroids were used in combination with azathioprine, a chemical derivative of 6-mercaptopurine, and after the discovery of antilymphocyte globulin (ALG) were included together in the standard protocol for immunosuppressants. This significantly improved the survival of the transplanted tissue, but at the same time caused a number of serious, particularly long-term, side effects. These

effects included infections, organ toxicity, metabolic disorders, slow wound healing, anemia, leukopenia, diabetes, osteoporosis, growth retardation in children and even an increased risk of malignancies. [6, 7]

Further advances in the understanding of immune processes led to the development of more selective therapies that provided better results and reduced the risk of side effects. Immunopharmacology, the third phase of immunosuppressive therapy, focuses on the selective regulation of specific subpopulations of immunocompetent cells. This approach is based on the development of agents or procedures with selective effects on the acquisition of immune reactivity, the recognition of immunogenic stimuli on cells with receptors, the induction of differentiation and maturation of lymphocytes, cellular interactions, and the modulation of effector functions. These strategies enable effective suppression of the immune response with minimal side effects. [6]

1.3. Characteristics of immunosuppressive therapy

The ideal immunosuppressant should possess several key properties that facilitate effective suppression of transplanted organ and tissue rejection while minimizing the risk of infection and adverse side effects. The following features are essential for an optimal immunosuppressive agent: [5]

- **Compatibility with Combination Therapy**: The ability to be effectively used in conjunction with other medications to reduce the frequency of rejection episodes, thereby enhancing overall therapeutic efficacy.
- **Selective Immunosuppression**: The capacity to prevent organ rejection without significantly increasing susceptibility to infections or causing other adverse effects, thereby maintaining a balance between immunosuppression and immune competence.
- **Reduction of Chronic Rejection**: The effectiveness in reducing chronic organ rejection, which is critical for the long-term survival and function of the transplanted organ.
- **Selective Antiproliferative Effect**: A preferential antiproliferative effect on lymphocytes, the primary mediators of immune response, while sparing other cell types, including hematopoietic cells, to reduce the risk of systemic toxicity.

- **Safety Profile**: The absence of hepatotoxicity, nephrotoxicity, or mutagenic effects, ensuring that the immunosuppressant does not cause significant harm to the liver, kidneys, or genetic material of the patient.

These attributes are crucial in developing an immunosuppressive therapy that not only effectively prevents rejection but also safeguards the patient's overall health and quality of life.

1.4. Therapeutic monitoring of immunosuppressants

Effective management of immunosuppressive therapy requires careful therapeutic drug monitoring (TDM) to ensure optimal therapeutic efficacy and minimize adverse effects. This monitoring is performed by assessing the drug concentration in the blood, which allows the dose and treatment to be adjusted to the individual needs of the patient. This prevents organ rejection and the side effects of immunosuppressive therapy. Interpreting the results of therapy monitoring requires a multidisciplinary approach, taking into account various factors that can influence the concentration of the drug in the body. [8]

There are several factors that influence the variability of drug concentrations in patients. These include the physiological characteristics of the patient themselves, such as body mass and metabolism, the presence of other drugs taken at the same time and external factors such as temperature, diet and environment. On the other hand, the characteristics of the drug itself, including the route of administration, quality and rate of absorption, will also affect its concentration.

Another approach to monitoring immunosuppressive drugs is simpler and involves monitoring the function of the transplanted organ in patients receiving the therapy. This is based on appropriate biochemical parameters and radiological examinations. Therapeutic monitoring adjusts the dose of the drug and the route of administration to the specific needs and characteristics of each patient, taking into account the differences between patients. [9,10]

1.5. Application of immunosuppressive therapy

Immunosuppressants are essential in the treatment of autoimmune diseases and the prevention of transplant rejection. Their primary applications encompass three fundamental areas: [4]

- **Prevention of Transplant Rejection:** Immunosuppressive drugs are crucial in preventing the rejection of transplanted organs such as liver, kidneys, heart and tissues.

By suppressing the recipient's immune response, these medications help to ensure the survival and proper function of the transplanted organ or tissue.

- **Inhibition of Graft-versus-Host Disease (GVHD):** These drugs are vital in inhibiting the graft-versus-host reaction, particularly in bone marrow transplants. GVHD occurs when the transplanted graft's lymphocytes react against the host's antigens. Immunosuppressive therapy mitigates this reaction, promoting tolerance and reducing complications associated with the transplant.
- **Treatment of Autoimmune Diseases:** Immunosuppressive therapy is also employed to manage various autoimmune diseases, which often involve a significant autoimmune component. These conditions include idiopathic thrombocytopenic purpura, myasthenia gravis, rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis, psoriasis, as well as particular forms of hemolytic anemia. In these diseases, immunosuppressants help to control the aberrant immune response that targets the body’s own tissues.

The proper use of immunosuppressive therapy requires careful monitoring and adaptation to the individual patient. Factors such as general health, drug tolerance and possible side effects must be carefully considered. The aim is to achieve an optimal balance between effective suppression of the immune response and minimizing the risk of infections and other complications.

2. CLASSIFICATION OF IMMUNOSUPPRESSIVE DRUGS

Immunosuppressive drugs have effects on lymphocytes through various mechanisms, including direct cytotoxicity, modification of lymphocyte turnover and inhibition of lymphocyte activation pathways. [1]

Depending on their mechanisms of action, they can be categorized into different groups: [1]

1. **Inhibitors of cytokine gene expression:** corticosteroids fall into this category and suppress the expression of genes responsible for cytokine production.
2. **Inhibitors of IL-2 production or activity:** Drugs such as tacrolimus and ciclosporin inhibit the production or function of interleukin-2 (IL-2), which is a crucial cytokine for the T cells proliferation.
3. **Purine and pyrimidine synthesis inhibitors:** Mycophenolate mofetil and azathioprine interfere in DNA and RNA synthesis by inhibiting the synthesis of pyrimidines and purines.
4. **Serine/threonine kinase inhibitors:** Sirolimus and everolimus inhibit serine/threonine kinases and interrupt signaling pathways that are essential for lymphocyte proliferation and activation.
5. **Blockers for T-cell surface molecules:** Monoclonal antibodies target and block surface molecules on T cells that are involved in the immune signaling process, preventing T cell activation.

Together, these different mechanisms contribute to the effective suppression of the immune response in various clinical contexts, including transplantation and autoimmune disease

The combination of these different mechanisms enables effective suppression of the immune response in the different clinical contexts, including transplantation and autoimmune diseases.

2.1. Corticosteroids

Corticosteroids, produced in the adrenal glands, are essential for a whole range of physiological roles in the body. The Nobel Prize in 1950 was given to Philip Hench, Edward Kendall and Tadeus Reichstein for their revolutionary findings of the function of the adrenal cortex. [11]

The most important natural corticosteroids are cortisol and aldosterone.

Synthetic corticosteroids, designed to mimic the effects of these natural hormones, are frequently used to treat immune system disorders, inflammatory diseases, and to regulate electrolyte balance in individuals who cannot produce sufficient natural corticosteroids. Typical examples of synthetic corticosteroids are methylprednisolone, dexamethasone, betamethasone, prednisolone, beclomethasone and clobetasol. [12]

Cortisol, a central glucocorticoid, is essential for regulating blood glucose levels and the metabolism of carbohydrates, fats, and proteins. Additionally, it significantly influences growth, reproductive functions, and brain activity. In normal conditions, the adrenal glands produce between 24 and 30 mg of cortisol per day, with high levels in the early morning hours. But in response to stress, cortisol production can increase up to 300 mg per day, which can have long-term effects on the hypothalamic-pituitary-adrenal gland axis. [13, 14, 15]

Aldosterone, a primary mineralocorticoid, is vital for maintaining water and electrolyte balance by promoting renal sodium retention and regulating extracellular fluid electrolytes. [13]

Historically, the use of corticosteroids in medicine was limited to the treatment of Addison's disease. Today, corticosteroids, both natural and synthetic, are essential in medical practice and are widely used for a variety of conditions because of their potent anti-inflammatory and immunosuppressive abilities. The strongest effect of corticosteroids appears about six hours after administration, with their pharmacological effect lasting up to 24 hours. However, despite their benefits, long-term use of corticosteroids can result in consequential side effects that require careful management to avoid permanent damage to the body. [16]

2.1.1. Mechanism of action of corticosteroids

Glucocorticoid receptors, expressed on various cell types, play a pivotal role in the regulation of various physiological processes. The release of hormones such as adrenocorticotropic hormone (ACTH), which is crucial for the initiation of cortisol synthesis, is modulated by complex interactions among neurons, endocrine factors, and cytokines. Once synthesized, the majority of cortisol binds to specific proteins in the blood, leaving a smaller fraction free and biologically active, which is subsequently converted into cortisone. [17]

Glucocorticoids act by passive diffusion through the cell membrane. After moving through the cell membrane, they attach to cytoplasmic receptors associated with the heat shock proteins Hsp90, Hsp70 (Hsp, heat shock protein) and the protein that binds FK506 (tacrolimus). The hormone-receptor complex is then formed and enters the cell nucleus. In the nucleus, this complex ties to specific DNA regions called GREs (glucocorticoid response elements) resulting in increased or decreased gene transcription. [14]

In this way, corticosteroids prevent the nuclear deviation of the transcription factors k-B (Nuclear Factor kappaB, NFk-B) and AP-1 (Activator Protein 1) and their association with the corresponding DNA sequences, thereby inhibiting the transcription of genes coding for various cytokines and preventing the proliferation and function of macrophages, neutrophils and fibroblasts. Consequently, the release and synthesis of pro-inflammatory cytokines such as interleukin-6, interleukin-1, and tumor necrosis factor-alpha (TNF-α) are significantly reduced. [3, 18, 19]

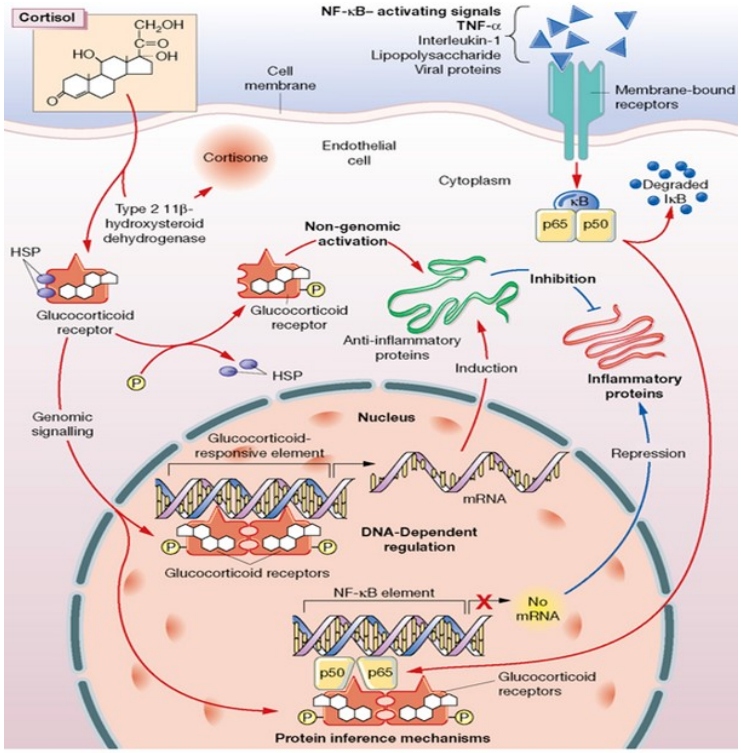

Figure 1. The mechanism of action of corticosteroids at the cellular level [20]

Glucocorticoids stimulate the making of anti-inflammatory proteins such as lipocortin and inhibit the activity of phospholipase A2, the enzyme responsible for catalyzing the conversion of phospholipids into arachidonic acid. This acid serves as a precursor for inflammatory products like prostaglandins, leukotrienes and thromboxane A2, which are the main mediators of inflammation (Figure 2). Corticosteroids prevent the synthesis of these potent inflammatory mediators and thereby reduce the signs and symptoms of inflammation. [21, 22]

In addition, they stabilize lysosomal membranes, reduce the release of inflammatory mediators from lysosomes and reduce capillary permeability, which prevents the passage of leukocytes. Corticosteroids also reduce the formation of bradykinin, a powerful vasodilator, and regulate the functions of fibroblasts and chondrocytes, reducing the release of enzymes that degrade cartilage and bone. These effects are crucial for the therapeutic improvement of patients with rheumatoid arthritis. [23]

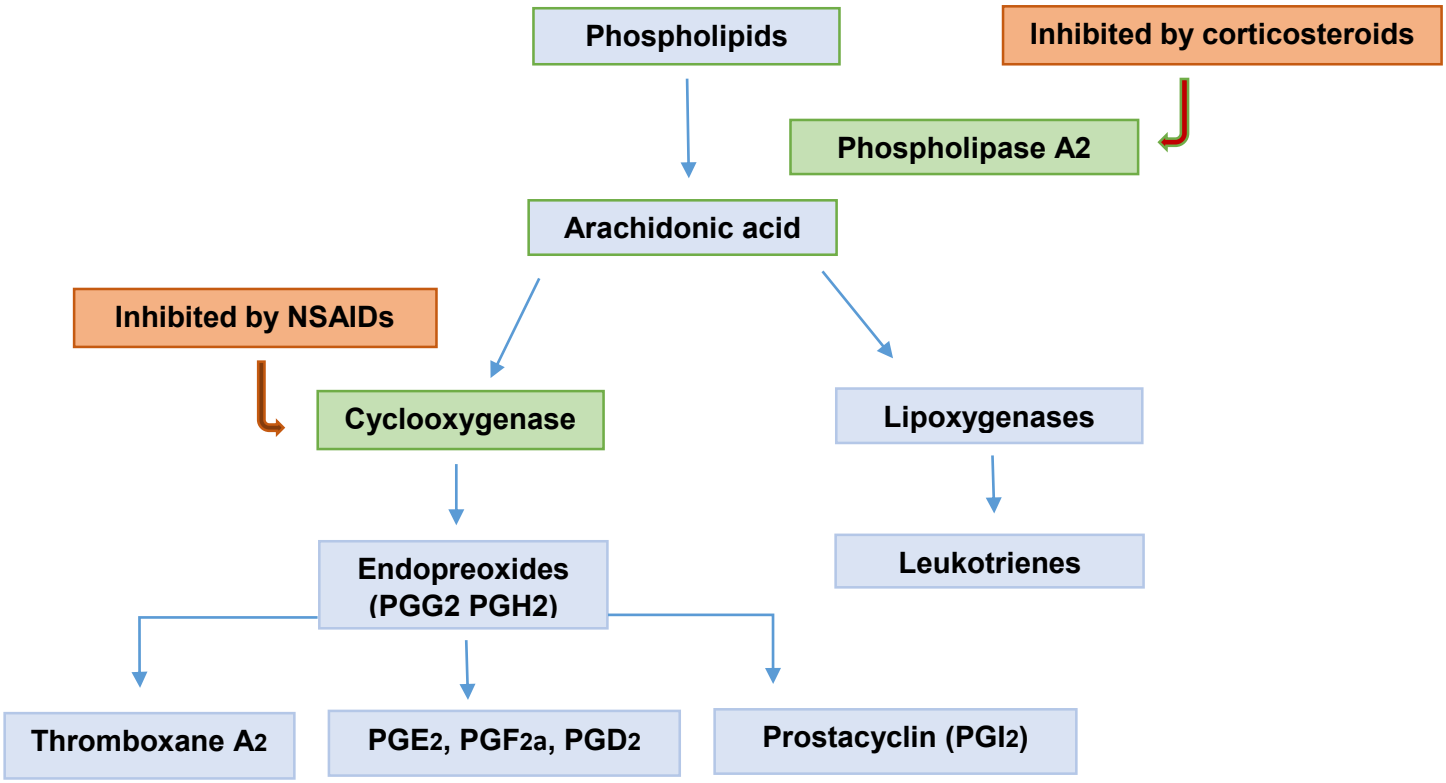

Figure 2. Regulation of inflammatory mediators by corticosteroids and NSAIDs

In addition to their anti-inflammatory properties, glucocorticoids play a vital role in immunoregulation. They reduce the number and activity of lymphocytes and monocytes in the circulation and inhibit lymphocyte proliferation. This immunosuppressive effect is particularly beneficial in the management of autoimmune diseases, where it helps mitigate the body's aberrant immune response.

Moreover, glucocorticoids exert significant influence on the metabolism of fats, proteins, and carbohydrates. They promote protein catabolism in muscle tissue, releasing amino acids for gluconeogenesis—the synthesis of glucose from non-carbohydrate sources.

All these physiological functions of glucocorticoids make them important regulators of the body's homeostasis and have important therapeutic effects in the treatment of various diseases.

2.1.2. Glucocorticoid receptor

The glucocorticoid receptor (GR), also known as NR3C1, is a receptor protein that binds and activates glucocorticoids. It is a member of the extensive family of transcription factors which are called nuclear hormone receptors. The human glucocorticoid receptor gene is located on the q arm of chromosome five and is expressed in almost every cell in the body, where it regulates genes that control metabolism and immune response. [24]

GR activation regulates gene expression through several mechanisms, including regulation of anti-inflammatory proteins in the nucleus or inhibition of anti-inflammatory proteins in the cytoplasm.

Structurally, the glucocorticoid receptor is a protein complex composed of multiple functional domains: N-terminal transactivation domain (TAD), a central DNA-binding domain (DBD), a C-terminal ligand-binding domain (LBD), and a flexible region that separates the LBD and DBD. When the glucocorticoids area absent, GR is localized in the cytoplasm, typically complexed with chaperone proteins such as the heat shock protein. After glucocorticoid binding, GR changes its conformation, becomes hyperphosphorylated, dissociates from other proteins, and translocates to the nucleus. From there, it regulates gene expression by binding to specific glucocorticoid response elements (GREs) and modulating both transactivation and transrepression processes. [24, 25]

During transactivation, GR dimers bind to specific GREs, stimulating the expression of genes that encode regulatory proteins with metabolic, anti-inflammatory, and immunosuppressive functions.

Conversely, transrepression involves the interaction of activated GR with pro-inflammatory transcription factors such as activator protein-1 (AP-1) and nuclear factor kappa B (NF-κB). By inhibiting these transcription factors from binding to DNA, GR suppresses the transcription of pro-inflammatory genes, thereby regulating the synthesis of proteins with anti-inflammatory and immunosuppressive effects. [26]

Thus, the glucocorticoid receptor plays a key role in regulating the expression of genes associated with metabolic processes, immune responses, and anti-inflammatory mechanisms. This regulatory function is essential for maintaining cellular homeostasis and modulating the body's response to physiological stressors and inflammation.

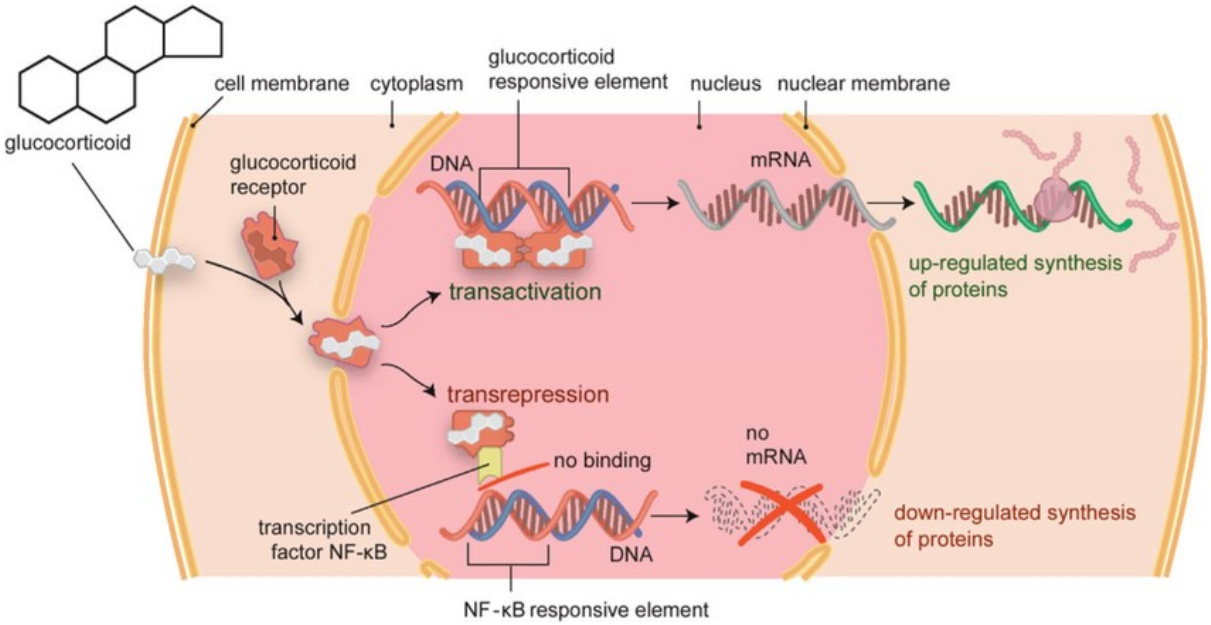

Figure 3. Mechanism of action of the glucocorticoid receptor [27]

2.1.3. Representatives of synthetic corticosteroids

Methylprednisolone

Methylprednisolone, known as Medrol, is a synthetic glucocorticoid that rapidly suppresses inflammation and modulates the immune response. In its anti-inflammatory effects it is five times stronger than hydrocortisone, with minimal mineralocorticoid activity. Methylprednisolone with its derivatives, methylprednisolone sodium and methylprednisolone acetate succinate, are primarily applied for their anti-inflammatory and immunosuppressive properties.

Upon administration, methylprednisolone diffuses across cell membranes and attaches to intracellular glucocorticoid receptors. This receptor-ligand complex transfers to the nucleus, where it combines with specific DNA sequences to either enhance or suppress gene transcription. It blocks pro-inflammatory gene promoters, upregulates anti-inflammatory gene expression, and inhibits inflammatory cytokine synthesis by interfering with transcription factors such as NF-κB. Additionally, methylprednisolone suppresses the synthesis of cyclooxygenase-2 (COX-2), reducing prostaglandin production and controlling the inflammatory response.

Methylprednisolone also influences various cellular processes: it reverses capillary permeability, suppresses fibroblast and leukocyte migration, regulates protein synthesis, and stabilizes lysosomal membranes. It particularly affects cell-mediated immune functions by decreasing the number of circulating lymphocytes, inducing neutrophilic leukocytosis, and reducing eosinophil and lymphocyte counts. Furthermore, it stimulates cell differentiation and promotes apoptosis in tumor cells.

Methylprednisolone can be applied orally with milk or food to reduce gastrointestinal side effects. Intramuscular injection should avoid the deltoid muscle to prevent subcutaneous atrophy and areas with acute local infection. Intravenous administration, particularly with high doses over 250 mg, requires careful monitoring due to risks of hypotension, cardiac arrhythmias, and sudden death if infused too rapidly (under 30 minutes). Methylprednisolone has around 88% oral bioavailability, with a half-life ranging from 0.25 to 5 hours depending on the route of administration, hepatic metabolism, and urinary excretion.

While effective in treating inflammatory conditions, methylprednisolone can cause a number of side effects. Serious adverse effects include decreased resistance to infection, arterial hypertension, osteoporosis, hyperlipidaemia and the appearance of acne. These side effects are more common with prolonged use or high doses and suddenly stopping treatment after prolonged use can trigger acute adrenal insufficiency. [28]

Methylprednisolone is primarily metabolized by the enzyme cytochrome P450 (CYP) 3A4, a dominant member of the CYP enzyme family in the adult liver. CYP3A4 catalyses the essential phase I metabolic reaction of 6β-hydroxylation of steroids, both endogenous and synthetic corticosteroids. This enzymatic process is crucial for the metabolism of glucocorticoids. Additionally, CYP3A4 metabolizes many other substances, including various drugs, which can modulate the metabolism of glucocorticoids by either inducing or inhibiting this enzyme.

CYP3A4 inducers are medications that stimulate CYP3A4 activity, leading to increased hepatic clearance and reduced drug concentrations. Drugs that lower drug levels include barbiturates, phenytoin, rifampicin, and carbamazepine.

CYP3A4 inhibitors, on the other hand, reduce CYP3A4 activity, resulting in decreased hepatic clearance and increased plasma concentrations of CYP3A4 substrates such as methylprednisolone. In the presence of CYP3A4 inhibitors, the dose of methylprednisolone should be adjusted to avoid steroid toxicity. Included in this group of medications are macrolide

antibiotics, grapefruit juice, oral contraceptives, and ketoconazole. In composition with non-steroidal anti-inflammatory drugs (NSAIDs) there is a risk of an ulcerogenic effect. [29]

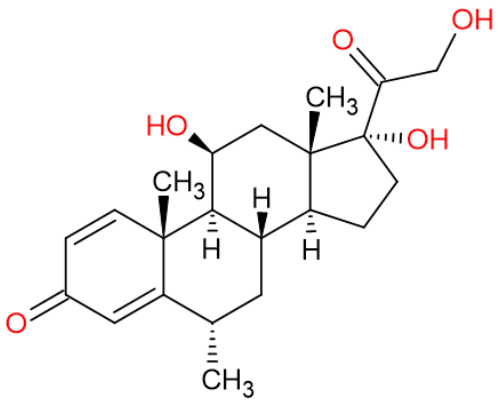

Figure 4. The chemical structure of methylprednisolone

Dexamethasone

Dexamethasone is a synthetic adrenal corticosteroid. It belongs to the group of glucocorticosteroids with a moderately strong effect. In its free form, passes through cell membranes and attaches with great affinity to some cytoplasmic glucocorticoid receptors. The resulting complex binds to DNA elements, leading to the synthesis of proteins that prevent the migration of leukocytes to sites of inflammation. Additionally, it disrupts NF-κB activation and apoptosis pathways.

Dexamethasone is administered orally, intravenously, intramuscularly or locally, depending on the indication and severity of the disease. It is used in various diseases such as rheumatoid arthritis, asthma, allergic dermatitis, autoimmune diseases and in the treatment of acute diseases like as acute allergic reactions, cerebral edema, severe forms of asthma and the like.

Dexamethasone is indicated for patients with severe COVID-19 who need supplemental oxygen or mechanical ventilation. However, doctors should not use it to medicate patients with mild to moderate COVID-19.

Commonly reported adverse effects include insomnia, acne, fluid retention, electrolyte imbalances, weight gain, altered appetite, nausea and depression. Additional risks encompass adrenal suppression, arrhythmias, spermatogenic changes, glaucoma, hypokalemia and

increased intracranial pressure. Hepatotoxicity, particularly with high doses, is a recognized concern due to hepatitis reactivation or hepatocellular injury.

Regarding contraindications, dexamethasone should not be used in patients with cerebral malaria, systemic fungal infections, or if they are hypersensitive to it. Patients with conditions such as cirrhosis, diverticulitis, myasthenia gravis, renal insufficiency, peptic ulcer disease, or ulcerative colitis require careful monitoring when prescribed dexamethasone. [30]

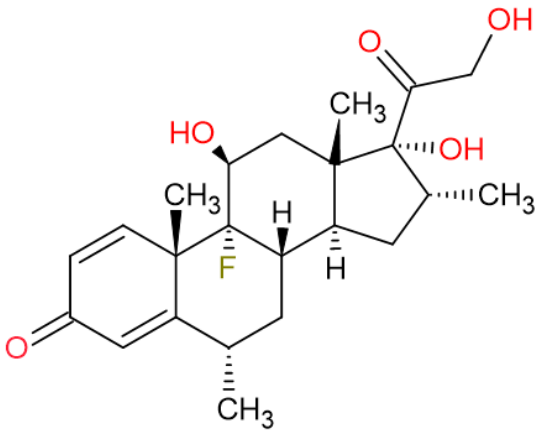

Figure 5. The chemical structure of dexamtehason

Beclomethasone dipropionacelte

Beclomethasone is a synthetic glucocorticoid with strong anti-inflammatory and vasoconstrictor effects. It was the first inhaled corticosteroid in the form of an aerosol to come onto the market. This is used to treat asthma, allergic rhinitis, chronic obstructive pulmonary disease (COPD) and other inflammatory diseases of the airways. The main advantage of beclomethasone dipropionate compared to other inhaled corticosteroids is its high local activity and lower systemic effects caused by metabolic inactivation of the ingested part of the dose.

Although inhaled beclomethasone is generally well tolerated, side effects such as throat irritation, fungal infections in the mouth (oral candidiasis) or coughing may occur, which is dose-dependent and more frequent in women compared to men. The risk of systemic side effects is generally lower with inhaled beclomethasone than with oral corticosteroids, but patients should be alerted to possible side effects. [31]

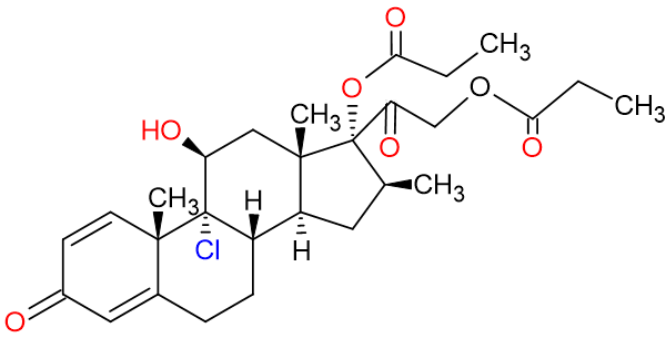

Figure 6. The chemical structure of beclomethasone dipropionate

Clobetasol propionate

Clobetasol propionate is a synthetic corticosteroid that belongs to the group of glucocorticoids with extremely strong anti-inflammatory, immunosuppressive and anti-mitotic effects. Through its action, it influences the expansion, differentiation and function of cells and inhibits cytokine development. The mechanism of action is the same as that of the corticosteroids described above. It is used to treat various dermatological diseases such as psoriasis, eczema, dermatitis, lichen ruber and other inflammatory skin diseases. [32]

It is applied topically in the form of a cream or lotion. The dosage depends on the condition of the skin and the patient's response to the therapy. As it is a highly effective corticosteroid, it is recommended that treatment is limited to two consecutive weeks. [33]

However, the efficacy of clobetasol propionate is associated with local side effects such as burning, redness, irritation and atrophy of the skin as well as systemic side effects like suppression of the hypothalamic-pituitary-adrenal axis and can lead to hormonal imbalances. Patients who apply it should be carefully instructed on how to use it. [32]

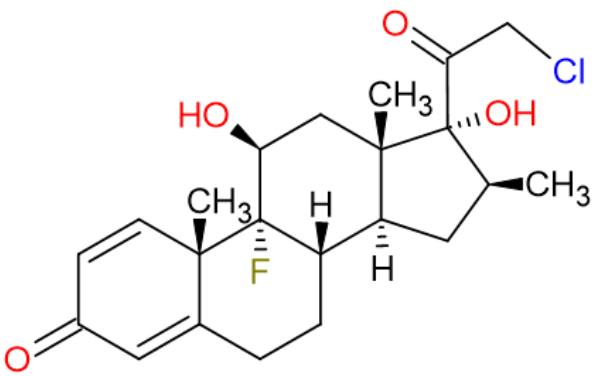

Figure 7. The chemical structure of clobetasol

2.1.4. Application of corticosteroids in dental medicine

In dental medicine, corticosteroids are applied in several forms - topical, local and systemic - to reduce the symptoms of the main disease or the patient's current condition.

The topical application of corticosteroids aims to prevent mast cell degranulation and reduce capillary permeability, thereby decreasing histamine release from basophils and mast cells and minimizing fluid extravasation. These drugs are used to treat pulp overgrowth, pulpotomy, dentinal hypersensitivity, and to mitigate inflammatory reactions, redness, and swelling in vesiculobullous and ulcerative diseases such as gingivitis, lichen planus, pemphigus vulgaris, erythema exsudativum multiforme, and aphthae. [34, 35]

The anti-inflammatory properties of corticosteroids are exhibited through the inhibition of inflammatory mediators and the stimulation of anti-inflammatory mechanisms. Additionally, their immunosuppressive effects reduce delayed hypersensitivity reactions by acting directly on T lymphocytes.

Systemic administration of corticosteroids is indicated in scenarios such as wisdom tooth extraction, pre-prosthetic procedures, reconstructive oral surgery, and orthognathic surgery. [34]

Patients with adrenal insufficiency who are on a stable corticosteroid regimen can generally tolerate routine dental procedures without requiring an increased dose of glucocorticoids. Minor oral and periodontal surgical procedures, including simple tooth extractions, soft tissue surgeries, and biopsies, do not typically precipitate an adrenal crisis in patients maintained on an appropriate dose of hydrocortisone (25 mg/day). Conversely, major oral surgical procedures, such as multiple tooth extractions, segmental periodontal surgery, maxillofacial surgery, and oral cancer surgery, necessitate an increased daily dose of hydrocortisone to 50 to 100 mg/day on the day of surgery and for one day post-surgery (24-48 hours), with the possibility of hospitalization for closer monitoring. [36]

Before using corticosteroids, it is crucial to rule out infections caused by microorganisms, especially viruses (such as herpes), where the use of corticosteroids is contraindicated. It is important to recognize that the immune response in patients taking corticosteroids may be compromised, and the wound healing process may be delayed, necessitating strict adherence to aseptic protocols.

Desquamative gingivitis

Desquamative gingivitis, together with ulceronecrotic gingivitis, is a disease with an alternative type of inflammation. This type of gingivitis is characterized by a particular localization. While ulceronecrotic and other forms of gingivitis are confined to the interdental and marginal gingiva, desquamative gingivitis is localized in the area of the fixed gingiva and can therefore also affect the interdental gingiva (Figure 8). This type of gingivitis is not caused by biofilm, but its etiology is reported to be unknown. It has been observed to occur in menopausal women, suggesting that hormonal imbalances may play a role in its development. Additionally, desquamative gingivitis is associated with certain systemic diseases, particularly dermatoses. [37]

It can manifest in three clinical forms:

The mild form is often discovered incidentally during routine dental examinations. Enanthematic zones are observed on the attached gingiva without epithelial desquamation, and changes at this stage are not accompanied by pain. This form of desquamative gingivitis most commonly occurs in young women. [37]

The moderate form is characterized by bright red and gray areas, especially on the attached gingiva. The epithelium is loosely attached to the substrate and detaches easily upon contact, exposing the gingival membrane, which bleeds easily and is painful upon touch. The Nikolsky phenomenon is positive. The remaining gingiva appears red and has a soft consistency. This moderate form most frequently affects women between the ages of 30 and 40. Patients experience mild pain and sensitivity to mechanical and thermal stimuli, making oral hygiene maintenance difficult due to pain sensitivity. [37]

The severe form is characterized by clearly defined, diffuse, irregularly distributed areas of desquamated epithelium. The exposed gingival membrane is covered with gray-blue zones, giving the gingiva a mottled appearance. In some areas, fluid-filled vesicles may also appear, which, when ruptured, leave eroded and painful fields. [37]

In this form of desquamative gingivitis, the changes are extremely painful. There is sensitivity to all external stimuli (mechanical, thermal). Patients report a dry mouth, with burning sensations throughout the oral cavity.

Therapy options for desquamative gingivitis can be either local or systemic, with corticosteroid preparations being the most commonly prescribed. For local application, customized splints are often employed to deliver corticosteroid gels directly to the affected areas. [37]

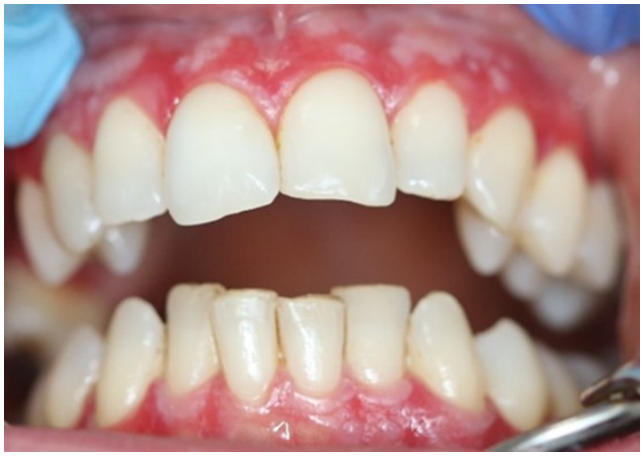

Figure 8. Desquamative gingivitis [37]

Lichen planus

Lichen planus is a chronic inflammatory disease of the mucous membranes and skin, characterized by the presence of lichenoid papules. The name "lichen planus" derives from the Greek word "lichen," meaning tree moss or lichen, and the Latin word "planus," meaning flat. Women are affected slightly more often than men, with a ratio of 3:2, with the majority of cases (approx. 70%) occurring between 30 and 60 years of age. Oral mucosal lesions are observed in 75% of patients who already have skin changes. Conversely, only 10-20% of those with initial manifestations in the oral mucosa will develop skin lesions. A common clinical presentation is the isolated form of lichen planus, which appears only on the oral mucosa. [38, 39]

The etiology of lichen planus is based on the interaction of various endogenous and exogenous factors. Commonly reported etiologic factors include stress, medications (such as antidiabetics, antirheumatics, antihypertensives, and hepatitis B vaccines), dental materials, hepatitis C virus infection, genetic predisposition, and autoimmunity. Studies have shown the presence of immunoglobulin deposits (IgG, IgM) and complement C3 in skin and oral mucosal lesions.

The primary clinical manifestation of lichen planus on the skin and mucous membranes is the papule. Papules are elevated lesions over the surface of the skin and mucous membranes, circular in shape, with a diameter of 0.5-1 mm and a smooth surface. On the skin, they appear reddish, while on the oral mucosa, they are grayish-white with a pearly sheen. Another key characteristic of lichen planus is its symmetry, with bilateral lesions on the skin and oral

mucosa. Lichen planus, as with any chronic disease, has phases of remission and exacerbation. [38]

Lichen planus of the oral mucosa can appear in six different forms: reticular, erosive, papular, plaque-like, atrophic, and bullous. The reticular and erosive forms are the most common. [39]

Reticular Lichen Planus: This form is named after the characteristic cluster of papules that are connected by interwoven white lines, creating a network or lace-like appearance (Wickham's striae). The interconnected papules are located on the enanthematous surface of the mucosa, elevated above the mucosal surface, and symmetrically distributed. The most common locations are the buccal mucosa (at the occlusal line), lateral tongue margins, and the retromolar region, although it can appear on any part of the oral mucosa (including the gingiva, as desquamative gingivitis). These lesions are generally asymptomatic and are sometimes diagnosed incidentally. [39, 40]

Erosive-Ulcerative Lichen Planus: Although less common than the reticular form, the erosive form is more significant for patients due to the symptomatic lesions in the oral cavity. These lesions are associated with varying degrees of pain and sometimes increased salivation, making speech, chewing, and swallowing difficult. Clinically, there are atrophic, enanthematous areas with centrally located erosions or ulcers of varying severity. The periphery of these atrophic areas is usually bordered by interconnected grayish-white papules in the form of streaks. Common locations include the buccal mucosa and soft palate, with symmetrical changes. [39, 41]

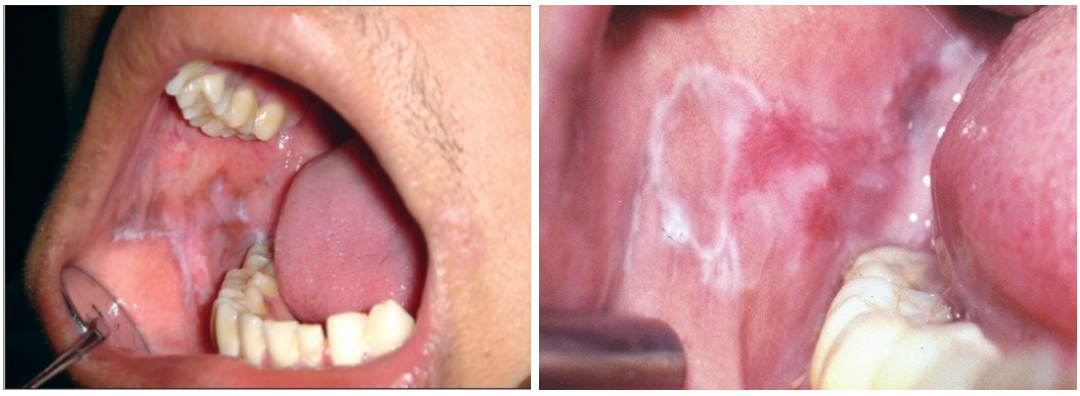

Figure 9. and 10. Reticular and erosive oral lichen planus on the buccal mucosa [42, 43]

The diagnosis of reticular lichen planus is often made based on medical history and clinical findings. The presence of a lichenoid network bilaterally on the buccal mucosa is practically pathognomonic. Diagnostic challenges may arise if secondary fungal infections alter the

clinical picture. Erosive lichen planus can be more difficult to diagnose due to the presence of erosive and ulcerative changes. In such cases, histopathological examination, involving a tissue biopsy, is necessary to rule out other ulcerative or erosive diseases. In some cases, direct immunofluorescence may be required for diagnosis. [39]

The reticular form of lichen planus is typically asymptomatic and usually requires no treatment. However, if candidiasis is present, patients may experience burning sensations, discomfort, or a bitter taste, necessitating antifungal therapy. The erosive form often requires appropriate treatment due to the associated oral pain. Corticosteroids are the first line of therapy. Topical corticosteroids are recommended, with the choice of medication depending on the lesion's location and clinical severity. Systemic corticosteroids are used if lesions are widespread on the skin and other mucous membranes, requiring consultation with specialists. If corticosteroids are ineffective, the second line of therapy is ciclosporin and tacrolimus, and other drugs such as retinoids, and other immunomodulators can be applied. In certain cases, cryotherapy, laser therapy, or surgical removal of lesions may be considered. [43]

Pemphigus Vulgaris

Pemphigus vulgaris (PV) is characterized by the compilation of intraepithelial blisters. Among chronic autoimmune mucocutaneous diseases it is the most common condition. The term "pemphigus" derives from the Greek word "pemphix," meaning blister or bubble. This relatively rare disease affects both genders, typically between the ages of 40 and 70. It has been observed to have an increased incidence in certain populations, such as Ashkenazi Jews, Mediterranean peoples (Greeks, Italians), and Asians (particularly Indians and Japanese), who exhibit a genetic predisposition. Some authors report that in approximately 68% of cases, the disease initially manifests in the oral cavity and can only appear on the skin and other mucous membranes after several weeks or months. It is generally accepted that oral lesions "appear first and heal last". [38, 45]

In pemphigus vulgaris the primary mechanism responsible for its specific intraepithelial blister is the attaching of IgG antibodies on the epithelial cell membrane to an antigen. What causes this excessive production of IgG antibodies is still not clear. Nevertheless, some exogenous factors, such as hormonal imbalances, medications, various infections, specific types of food, and stressful situations, can activate this autoimmune reaction under specific conditions. [38]

Clinically, the primary lesion is a blister with a thin roof that ruptures very quickly, resulting in the formation of an eroded surface with a circular shape when the blisters occur individually.

However, the blisters can merge and form larger eroded areas and ulcers of different sizes and shapes. The mucosa under and around these lesions is erythematous and edematous. These changes in the mucosa heal very slowly, and new lesions appear in the meantime, complicating the clinical picture. Any area of the oral cavity can be affected, but most commonly the mucous membranes of the lips, ventral surface of the tongue, cheeks and gingiva. The pain almost always occurs spontaneously in the oral cavity, along with discomfort, a burning sensation, unpleasant odor, increased salivation and pain when speaking, chewing and swallowing, which over time leads to dehydration, weight loss and malnutrition. [38]

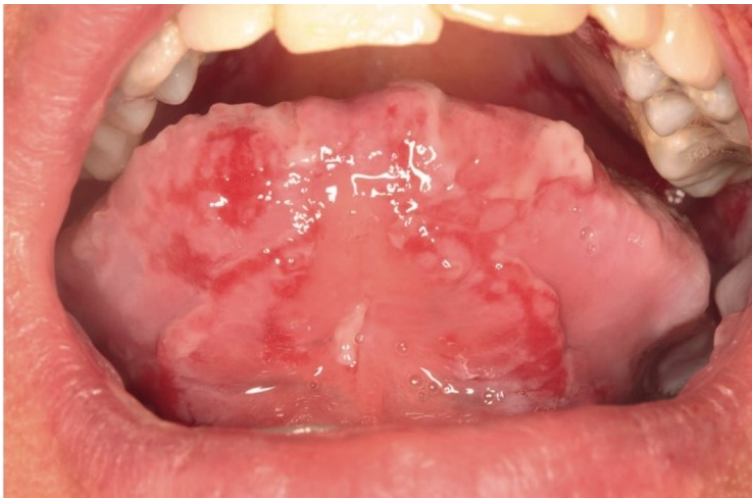

Figure 11. Pemphigus vulgaris as shallow, irregular red erosions of the ventral tongue with ulcers and tissue tags [38]

The diagnosis of pemphigus vulgaris is based on a thorough medical history, clinical examination, histopathological analysis, and direct and indirect immunofluorescence. Clinical examination typically reveals eroded surfaces with epithelial tags secondary to ruptured blisters, often distributed throughout the oral mucosa. Additionally, the Nikolsky sign is positive.The differential diagnosis of pemphigus vulgaris of the oral mucosa commonly includes other bullous dermatoses such as pemphigoid, herpetiform dermatitis, erythema multiforme, bullous lichen planus, as well as herpetic gingivostomatitis, aphthous ulcers, and other similar conditions. [38, 46]

Early confirmation of pemphigus vulgaris is crucial for effective disease management. The therapeutic approach is multidisciplinary, involving specialists from various disciplines, including oral medicine doctors.

Pemphigus vulgaris is a systemic disease, so treatment consists primarily of systemic therapy. Currently, corticosteroids are practically essential in therapy, often in combination with other immunosuppressive drugs. The standard treatment protocol begins with relatively high doses of systemic corticosteroids, which are gradually reduced to the lowest dose required to control the disease. This therapeutic strategy can achieve complete remission, although patients may experience periods of exacerbation and remission throughout their lifetime. In addition to this primary therapy, good oral hygiene and the use of mild antiseptic solutions with chlorhexidine or benzydamine are recommended. [38]

Erythema Exudativum Multiforme

Multiform Erythema (EEM) is an acute, recurrent inflammatory condition affecting the skin and mucous membranes. It presents with a variety of morphological and clinical manifestations such as macules, papules, vesicles, bullae, erosions, ulcers, and more, hence the term "multiforme," indicating its polymorphic nature. The severity of the condition can range from mild forms to severe diseases like Stevens-Johnson Syndrome (SJS) or the most extreme Epidermal Necrolysis (TEN) or Lyell's Syndrome.

Although the exact cause remains unclear, a multitude of agents, such as drugs (antibiotics, nonsteroidal anti-inflammatory drugs, anticonvulsants, sulfonamides), infections (often caused by the herpes simplex virus (HSV)), allergies, radiation, endocrine factors, immunological disorders, physical factors, and others, can trigger this condition. Multiform erythema predominantly influences young adults between 20 and 40 years of age, with men being more often affected than women. [47]

Multiform erythema usually has an acute onset and can exhibit a wide range of clinical manifestations. Prodromal symptoms include weakness, fever, headache, and muscle pain, occurring approximately seven days before the appearance of clinical changes on the skin and/or mucous membranes. It is estimated that about 40-60% of those affected with multiform erythema exhibit oral manifestations.

The disease typically first appears on the skin of the extremities, particularly the palms, soles, elbows, and knees, with symmetrical red macules and papules. These circular abrasions are miniature and can get bigger centrifugally, and within a period of day or two they can stretch out to 1-2 cm. The center turns out cyanotic, creating a specific "target" appearance. Over time, these changes may evolve into bullae with a necrotic center. Skin lesions are usually asymptomatic or associated with itching.

Changes in the oral cavity begin as enanthematic macules that also enlarge and spread peripherally, quickly progressing to vesicles or bullae. After rupturing, they leave eroded or ulcerated surfaces covered with necrotic pseudomembrane, irregular in shape and size, surrounded by an irregular and jagged edge. The mucosa around these lesions is enanthematic and edematous. Commonly affected areas include the vermilion, labial, buccal, and soft palate mucosa, as well as the dorsal and ventral surfaces of the tongue and the floor of the mouth. The tongue is enlarged, with enanthems on which vesicles and bullae appear. After rupturing, eroded surfaces covered with necrotic deposits remain. These lesions are very uncomfortable, causing patients to complain of discomfort, burning sensation, and intense pain. Sometimes, patients become dehydrated as they are unable to intake fluids due to the pain in their mouths. The gingiva and hard palate mucosa are relatively spared from these pathological changes. [47, 48]

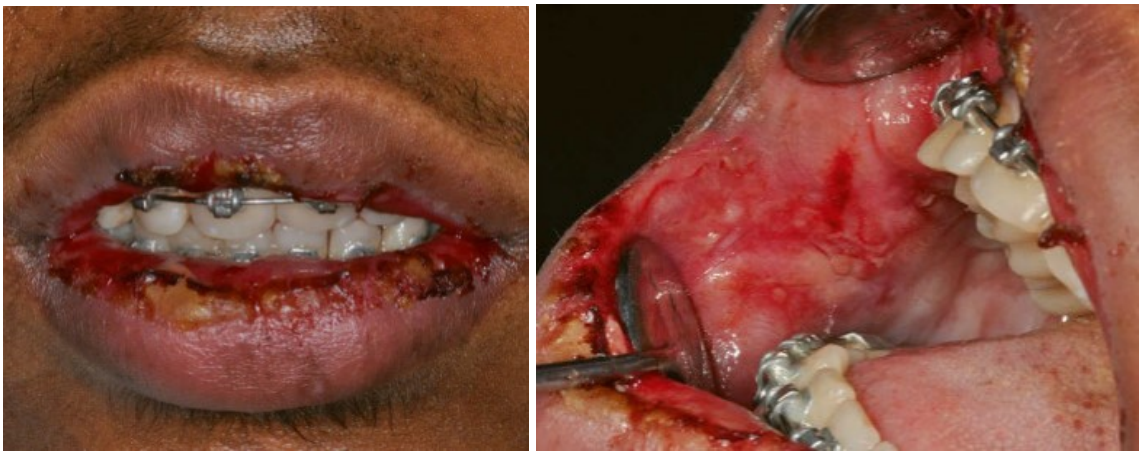

Figure 12. and 13. Oral lesions in erythema multiforme [49]

Stevens-Johnson Syndrome is acknowledged as an extreme form of multiform erythema, primarily affecting the mucous membranes of the mouth, eyes, and genital organs. The prodromal stage usually precedes clinical changes in the mucous membranes. Always affected is the oral mucosa, with extensively formed bullae succeeded by eroded surfaces covered with a white-grayish necrotic layer or a hemorrhagic pseudomembrane on the vermilion. Erosions can amplify to the esophagus, larynx and respiratory system. [50]

Diagnosis of multiform erythema is made by a dentist and dermatologist, but specialists from other fields may be involved depending on the dominant clinical manifestations. Diagnosis is primarily founded on a detailed medical history, clinical examination, and clinical presentation. Histopathological findings are not specific for multiform erythema. Diagnosing can sometimes be challenging due to similar clinical manifestations in the oral cavity in viral

stomatitis, pemphigus, pemphigoid, and other bullous dermatoses. Multiform erythema should also be differentiated from Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (TEN). [47]

If pathological changes are localized only in the oral cavity, a dentist can provide causal and symptomatic therapy. Multiform erythema associated with HSV requires the use of an antiviral agent (acyclovir, valacyclovir, famciclovir) orally. Medications or other allergens that caused the disease must be discontinued. Symptomatic therapy is based on the application of local corticosteroid therapy (solution, spray, ointment, orabase), which reduces subjective symptoms and objective signs of the disease. It is always beneficial to use a mild antiseptic mouthwash containing chlorhexidine to improve oral hygiene, prevent possible secondary infection, and more. If pathological changes are also present on the skin, therapy is prescribed by a dermatologist. In this case, systemic corticosteroids are used. Patients with severe forms of multiform erythema are hospitalized and require special care and treatment. [47]

Pemphigoid mucosae oris

Pemphigoid is a human autoimmune disease that can affect a skin and mucous membranes. It can occur in individuals of all ages, but it is most commonly seen in older adults. There are several types of pemphigoid, depending on the affected body part and the timing of onset: bullous pemphigoid (pemphigoides bullosus), gestational pemphigoid (pemphigoides gestationis), and cicatricial pemphigoid (pemphigoides cicatricialis, pemphigoides mucosae oris). Oral mucosal pemphigoid is a chronic autoimmune blistering disease. Damage to the oral mucosa results in epithelial atrophy and sometimes scarring (cicatrix – scar), hence the name pemphigoides cicatricialis. The disease occurs more often in women than in men.

The oral mucosa is almost always affected, and, the disease begins in the oral cavity in 95% of cases. Clinically, it is very difficult to distinguish pemphigoid from pemphigus, but the suffix "-oid" indicates that there is indeed a difference and that this condition only resembles pemphigus. [51]

The exact cause of pemphigoid is unknown as it is known to be an autoimmune disorder. An autoimmune reaction comes about when the body's natural defense mechanism (antibodies) begins to attack healthy cells for no known reason. The autoantibodies formed in this process damage the basal membrane zone of the epithelium. At this site, the epithelium separates from the subepithelial layer, forming a subepithelial blister. Some authors believe that in certain

cases there is a genetic predisposition, but factors such as immunological imbalance, genetic factors, and external factors may influence the onset of pemphigoid.

Pemphigoid of the oral mucosa begins with the appearance of blisters, which can occasionally be seen. Due to various traumas in the oral cavity (speaking, chewing, swallowing), the blister soon ruptures, leaving a large, circular eroded surface with patches of epithelium at the edge of the erosion. The eroded surface heals slowly, forming a scar. The surrounding mucosa is often unchanged. Blisters can appear on any part of the mucosa, but most commonly on the gingiva, buccal mucosa, and soft palate. The disease often entirely affects the gingiva in the shape of desquamative gingivitis. Oral lesions are clearly demarcated and solitary, rarely confluent. Subjective symptoms are mildly expressed as pain or a burning sensation.

Blisters can also appear on other mucous membranes. Lesions in the eye can manifest as conjunctivitis, corneal damage, dry eyes, and progressive scarring, which can lead to blindness. Rarely, other mucous membranes (genital organs, nose, pharynx) can be affected. Skin lesions occur in about 10-30% of cases, most commonly on the scalp, face, and neck. [51, 52]

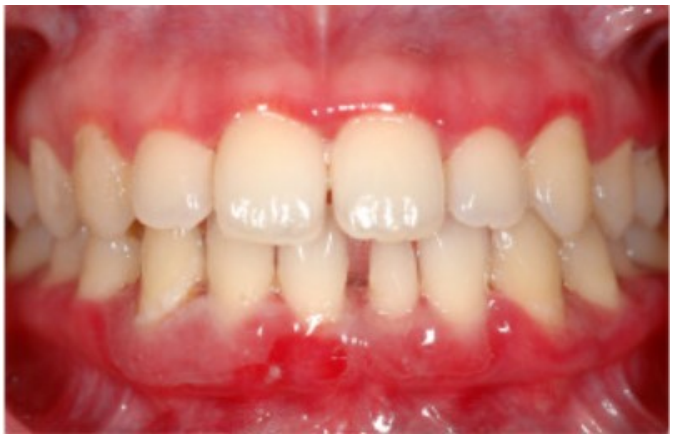

Figure 14. Oral mucous membrane pemphigoid at upper and lower labial and buccal gingiva [51]

The diagnosis of pemphigoid is found on anamnesis, immunopathological, histological and clinical findings. Anamnestically, it is identified as a chronic disease accompanied by the appearance of blisters without significant subjective symptoms. Clinical examination of the oral cavity reveals, in most cases, a secondary eroded surface as a result of blister rupture on clinically healthy mucosa. Intact blisters on the mucosa are very rarely seen as they easily rupture due to oral muscle movements. Lesions are covered with whitish fibrinous deposits, and the edge of the lesion usually has a red inflammatory zone. [51]

It is a symptom of few conditions and diseases such as , Stevens-Johnson syndrom, pemphigus vulgaris, linear IgA disease, bullous pemphigoid, erythema multiforme, and erythematous lupus.

The therapy of pemphigoid is multidisciplinary and depends on the severity of symptoms and signs, localization, and other factors. When lesions are confined to the oral mucosa, treatment involves local (creams, ointments, mouthwash) and intralesional corticosteroid application. Trearment with topical steroids of desquamative gingivitis is the most common, but in a soft dental splint covering the gums. If this therapy is unsuccessful, the application of tetracycline, doxycycline, or minocycline is usually beneficient in controlling desquamative gingivitis and other diverse oral lesions. Once disease control is achieved and healing occurs, local medication application can be discontinued until exacerbation occurs. There is no single therapy for all pemphigoid patients. Depending on the type of symptoms, disease activity, and lesion distribution, treatment is individualized. [51]

Recurrent aphthous stomatitis

Recurrent aphthous stomatitis (RAS) is an inflammatory, non-infectious condition of the oral mucosa, which is identified by repeated ulcerations in non-keratinized areas. The phrase"aphthous" is derived from the Greek word "aphtha," which menas "ulcer". The occurrence of aphthae is unpredictable and may alternate with periods of remission.

RAS is often associated with genetics, as evidenced by family history. The exact cause of aphthae is still undisclosed, but recent research points to the role of lymphocytic cytotoxicity and cell-mediated cytotoxicity that is antibody-dependent. Increased T lymphocyte cytotoxicity towards epithelial cells in patients with recurrent aphthae was proven in recent studies. Factors contributing to the development of aphthae include anemia (iron, folic acid and vitamin B12 deficiency), hormonal imbalances, stress, anxiety, minor mucosal injuries, spicy foods, gastrointestinal diseases, and autoimmune disorders. [53]

Aphthous stomatitis can manifest in three formations: minor aphthae, major aphthae, herpetiform aphthae. [53]

Minor Aphthae: These are the most often form, characterized by the recurrence of one or more small, painful, shallow, yellow-gray oval ulcers on the mucosa. These ulcers are usually covered with a fibrinous membrane, distinctly separated from the surrounding healthy mucosa,

and measure 3 to 10 mm in diameter. They typically mend without scarring within 7 to 10 days. They occur in non-keratinized mucosal areas, excluding the gingiva and hard palate.

Major Aphthae: These are painful ulcers larger than 10 mm in diameter, lasting from 3 to 4 weeks, and can affect keratinized mucosa, leaving scars after healing. They are characteristically irregular in shape, appearing unilaterally with a necrotic base. The edges are raised, red, and clearly demarcated from the surrounding healthy tissue. Pain and lymphadenopathy are present.

Herpetiform Aphthae: These are multiple, extremely painful erosions of grayish-white color, measuring 1-2 mm in diameter, affecting non-keratinized mucosa. They resemble herpes lesions but, unlike herpes, they lack prodromal systemic symptoms, gingivitis, or vesicles, and frequently recur.

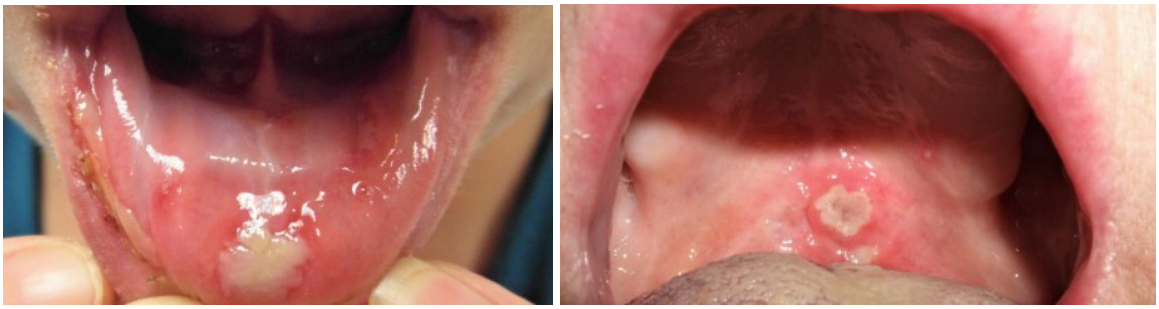

Figure 15. and 16. Recurrent aphthous stomatitis on mucous membrane of the lip and on the soft palate [54]

The first-line treatment for recurrent aphthous stomatitis (RAS) are the topical corticosteroids.. In combination with antiseptics,topical anesthetics and barrier agents they supply pain relief and decrease the frequency and duration of flare-ups. Even though it takes few days before they perform, they are more efficacous if applied at the beginning of an episode. Application should be multiple times a day, by preference after teeth cleaning and before sleep. Patients should be advised not to eat for at least half an hour after application.

Second-Line Treatment: For patients who do not respond to intermittent treatment with systemic corticosteroids alternative systemic agents should be considered, also for those who who cannot undertake corticosteroid treatment for some reasons. Additionally, supplementation with iron, folic acid, and vitamin B12 is essential in the treatment regimen. [54]

Behçet's disease

At first Behçet's disease (BD) was reported by the Turkish dermatologist Hulusi Behçet as a triplet of symptoms involving recurrent aphthous ulcerations in the mouth, genital ulcerations, and ulcerations on the mucous membranes of the eyes. Today, it is considered a systemic disease of unknown etiology, with vasculitis playing a crucial role in its pathogenesis, explaining its diverse manifestations in different tissues and organs including joints, central nervous system, blood vessels, and intestines. [38, 55]

BD is characterized by neutrophil hyperactivity with increased chemotaxis and elevated proinflammatory cytokines IL-8 and IL-17, where TNF-α plays a major role in pathogenesis. The HLA-B51 genotype is most commonly associated with BD. [38]

Oral manifestations present as ulcerations similar to aphthae, with red borders and significant pain, being the most commonly affected area in Behçet's syndrome. Genital lesions appear as ulcerations on the scrotum and vulvovaginal region.

Eye involvement can manifest as photophobia, conjunctivitis, uveitis, keratitis, iritis, and blindness. [38]

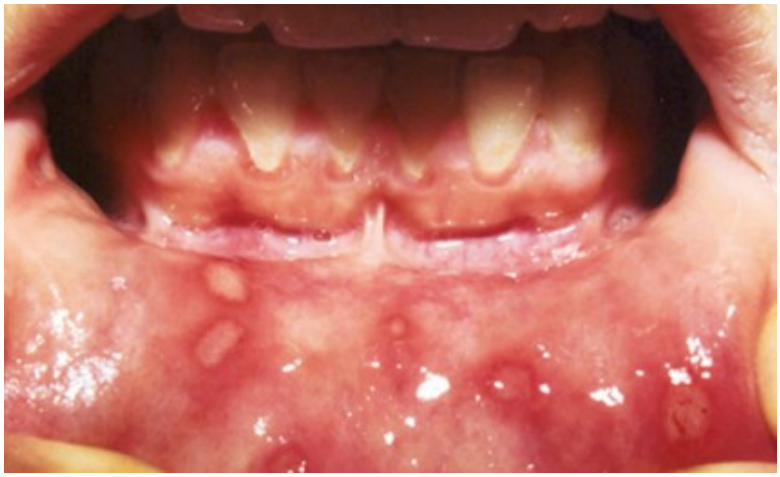

Figure 17. Oral Apthen bei Behçet-Syndrom [55]

Immunosuppressive therapy aims to modulate immune cell activity. During acute phases, intensive therapy with corticosteroids combined with other immunosuppressive drugs is used. Local corticosteroid application may be beneficial in mild cases where manifestations are limited to mucous membranes. [38, 55]

Behçet's disease calls for a multi-skilled approach involving rheumatologists, ophthalmologists, and other experts due to its systemic nature and potentially severe complications. Early detection and aggressive management are the key to improved outcomes and reduced disease progression.

2.1.5. Side effects of corticosteroids in the oral cavity

As we know, glucocorticoid therapy can cause various side effects, and the severity and frequency are usually associated with the length of therapy and drug dose.

Xerostomia

Xerostomia is a medical term that describes the condition of a dry mouth caused by reduced salivary gland secretion. Normal daily saliva production ranges from 0.5 to 1.5 liters and saliva flow rate that is not stimulated is usually around 0.3 ml/min, decreasing to 0.1 ml/min while sleeping and increasing to 4.0 ml/min during stimulating activities such as chewing and eating. [38, 56]

Clinical manifestations include inflamed mucosa, epithelial atrophy, and ulcerations. Saliva production is characterized through thick, sticky, and viscous saliva. Insufficient production and altered composition of saliva lead to changes in pH, which can promote caries , especially in the cervical areas, and increase the risk of oral infections. [38]

Patients with this disease often complain of general oral discomfort, dryness, tongue pain, poor denture adhesion, changes in taste perception, difficulty chewing, speaking and eating. [38]

Candidiasis

Oral candidiasis is a fungal infection of the oral cavity caused by Candida, a group of yeast fungi. Candida albicans is the most common cause of this infection. [3] Other species such as C. glabrata, C. guilliermondii, C. krusei, C. parapsilosis and C. Tropicalis can also occur. These fungi are opportunistic, meaning they strike when the immune system is weakened due to systemic disorders or immune system changes. [57]

Oral candidiasis often appears as a side effect of corticosteroid therapy, affecting a significant portion of patients treated with these medications. Typical symptoms include white, cheesy patches on the inside of the cheeks and tongue, accompanied by bad breath. Scraping off these patches reveals red and painful areas underneath. The likelihood of developing oral candidiasis increases with the use of strong liquid corticosteroids, prolonged treatment duration, and high

medication concentrations. For asthma patients using corticosteroid inhalers, it's crucial to rinse the mouth immediately after inhalation to prevent the corticosteroid from lingering on the mouth lining, which reduces the risk of developing candidiasis. Early identification and treatment are vital to managing symptoms and preventing complications associated with this fungal infection. [57, 58]

Hypogeusia

Corticosteroids can impact the sense of taste, leading to hypogeusia, a reduction in taste sensitivity. This is one of the possible side effects of taking these drugs.

The mechanism that corticosteroids may affect the sense of taste is not fully understood, but it is believed that these drugs may alter the structure and function of taste receptors on the tongue or in the brain, modify blood flow, or affect the function of nerve fibers that transmit taste information to the brain. [59, 60]

Hypogeusia presents a significant challenge for patients on corticosteroid therapy, potentially resulting in decreased appetite, altered eating habits, and weight loss. It is important to note that hypogeusia may be temporary or may decrease after discontinuation of the medication, but in some cases may be long-lasting or even permanent. [59, 60]

Patients who recognize changes in their sense of taste during corticosteroid therapy should consult with their doctor to review possible strategies to manage this side effect and possibly adjust therapy.

Oral leukoplakia

Oral leukoplakia is characterized by white patches or deposits on the mucous membrane of the mouth, a condition that cannot be scraped off. According to the World Health Organization (WHO), it is defined as " A white deposit that may be of suspected risk for cancer, excluding known diseases or disorders that increase the risk of cancer ". This pathological change primarily affects mature and older individuals. [61]

The development of oral leukoplakia is multifactorial and often idiopathic, though various factors can contribute. These white hyperkeratoses typically appear on the tongue's edges and tip but can extend to cover the entire tongue surface, inner cheeks, soft palate, throat, and esophagus. [62]

Clinically, oral leukoplakia manifests in different forms, including homogeneous, non-homogeneous, and hairy leukoplakia.

Homogeneous leukoplakia is characterized by uniform, white, thin patches that have a smooth or slightly wrinkled surface. These lesions are usually well-defined and asymptomatic, making them often unnoticed by patients. The risk of malignant transformation in homogeneous leukoplakia is generally lower compared to its non-homogeneous counterpart. However, the exact risk can vary depending on factors such as the size, location, and duration of the lesion, as well as patient-specific factors like tobacco use and alcohol consumption. [63]

Non-homogeneous leukoplakia presents a more varied and concerning clinical picture. It is characterized by mixed white and red areas, with a nodular, verrucous, or speckled appearance. These lesions are more likely to be symptomatic, presenting with discomfort, a burning sensation, or ulceration. The non-homogeneous nature signifies a higher risk of dysplasia and malignant transformation. Within this category, verrucous leukoplakia, which features a warty surface, and speckled leukoplakia, characterized by intermixed red and white areas, are particularly notable for their increased oncogenic potential. The management of non-homogeneous leukoplakia often involves more aggressive monitoring and intervention, including biopsy for histopathological assessment and possible excision. [63]

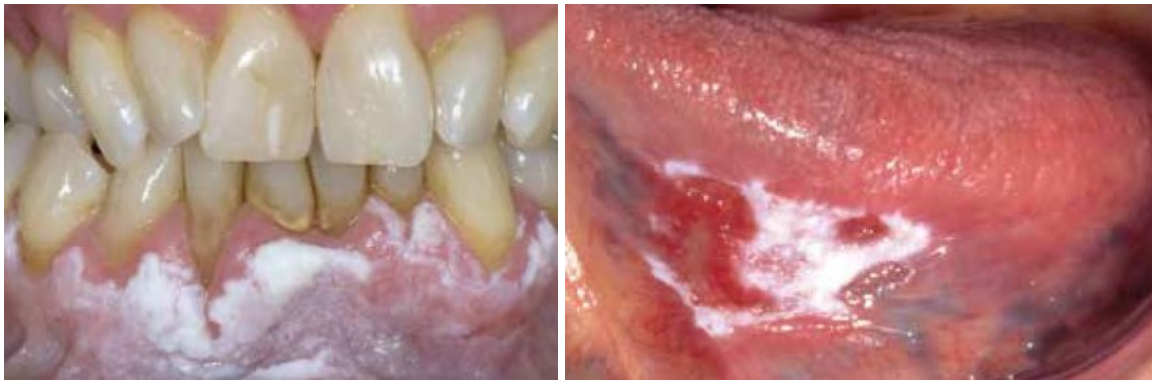

Figure 18. and 19. Homogeneous and non-homogeneous leukoplakia [63]

Hairy leukoplakia is a distinct entity typically associated with immunocompromised states, most notably HIV infection. It manifests as white, corrugated patches, usually located on the lateral borders of the tongue. Unlike homogeneous and non-homogeneous leukoplakia, hairy leukoplakia is stimulated by Epstein-Barr virus (EBV) infection. It does not carry a risk of malignant transformation but serves as an important clinical indicator of immunosuppression.

The management of hairy leukoplakia primarily involves addressing the underlying immunocompromised state, and antiviral therapies may be used to reduce lesion prominence. [64]

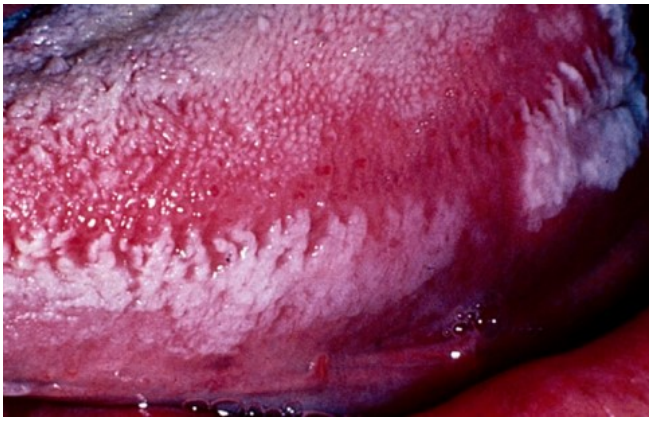

Figure 20. Hairy leucoplakia [65]

Diagnosis is crucial to distinguish oral leukoplakia from other oral mucosal changes and assess the potential for malignant transformation. Methods include clinical examination, microbiological, pathohistological, and immunological evaluations.

Treatment approaches are individualized and may involve removing potential sources of irritation, antifungal therapy if fungal infection is present, and anti-inflammatory agents. Lesions at high risk of malignancy may require surgical removal.

Prevention focuses on reducing recurrence and progression through education on oral hygiene, cessation of harmful habits such as smoking and alcohol consumption, regular dental check-ups, and systemic therapy with vitamins A, E, and B complex preparations. [62]

This comprehensive approach underscores the importance of early detection, tailored management, and ongoing monitoring to mitigate the risks associated with oral leukoplakia.

2.2. Calcineurin inhibitors

Calcineurin is a nuclear, calcium-calmodulin-dependent protein phosphatase with a central function in the translation of calcium signals into cellular responses. It regulates immune responses, cell differentiation, and various physiological functions. Structurally, calcineurin consists of two subunits: calcineurin A, which contains a dinuclear metal center in its active site, and calcineurin B, a myristoylated subunit that binds calcium. It is strongly inhibited by immunosuppressant drugs like cyclosporin A and FK506, which bind to immunophilin proteins. [66]

Dysregulation of calcineurin activity is linked to diseases such as cardiac hypertrophy, autoimmune disorders, and neurological conditions, underscoring its role in maintaining cellular function and homeostasis. Activation of calcineurin in T cells is pivotal for initiating immune responses and plays a crucial role in T cell proliferation and differentiation upon antigen stimulation. Understanding calcineurin's functions is crucial for developing therapies that can effectively modulate immune responses and neuronal activities, particularly in autoimmune diseases and neurodegenerative disorders. [66, 67]

The introduction of calcineurin inhibitors (CNIs) into clinical practice in the early 1980s marked a significant advancement in immunosuppressive therapy following organ transplantation. Cyclosporin A (CsA), the the first and exemplary representative of this class, was isolatedin 1970 from the fungus *Tolypocladium inflatum* by researchers at the Sandoz laboratory (now Novartis), led by Drs. Sandor Lazary and Jean-Francois Borel.

Successful human trials enabled its extensive use in kidney transplant patients as early as 1980. After dose adaptations, the first reports of fatal side effects decreased, while post-transplant survival rates increased dramatically. [68]

In 1984, *Streptomyces tsukubaensis*, another soil bacterium, provided scientists at the Japanese pharmaceutical company Fujisawa with an additional immunosuppressant. Its original name, FK-506, was later changed to Tacrolimus (derived from Tsukuba macrolide immunosuppressant). Tacrolimus has generally demonstrated superior efficacy and a more favorable side effect profile compared to CsA, thereby establishing itself as a preferred choice in clinical settings. [68]

2.2.1. Mechanism of action of calcineurin inhibitors

The mechanism of action of calcineurin inhibitors (CNIs) is based on the reduction of T-cell activity through the blocking of calcineurin, which is calcium/calmodulin-dependent serine/threonine phosphatase crucial for regulation of immune system. To attain an immunosuppressive effect, CNIs attach to a class of cytosolic protein receptors called immunophilins with high affinity: Cyclophilins regarding CsA and FK-binding protein-12 regarding of tacrolimus. CNI-immunophilin complexes attach to calcineurin and block its activity. [66, 67]

Inhibition of calcineurin in T cells prevents the dephosphorylation and subsequent activation of the nuclear factor of activated T-cells, cytoplasmic 1c (NFAT1c). The resulting inactivity of NFAT1c leads to a decreased synthesis of several key cytokines and immune response mediators, including interleukin-2 (IL-2), IL-3, IL-4, IL-5, tumor necrosis factor-alpha (TNF-α), CD40 ligand (CD40L), granulocyte-macrophage colony-stimulating factor (GM-CSF), and interferon-gamma (IFN-γ). [69, 70]

Additionally, tacrolimus and pimecrolimus inhibit the activation of mast cells and neutrophils as well as discharge of inflammatory mediators. Tacrolimus also influences the function of basophils and eosinophils and the function and induction of Langerhans cell apoptosis. [69]

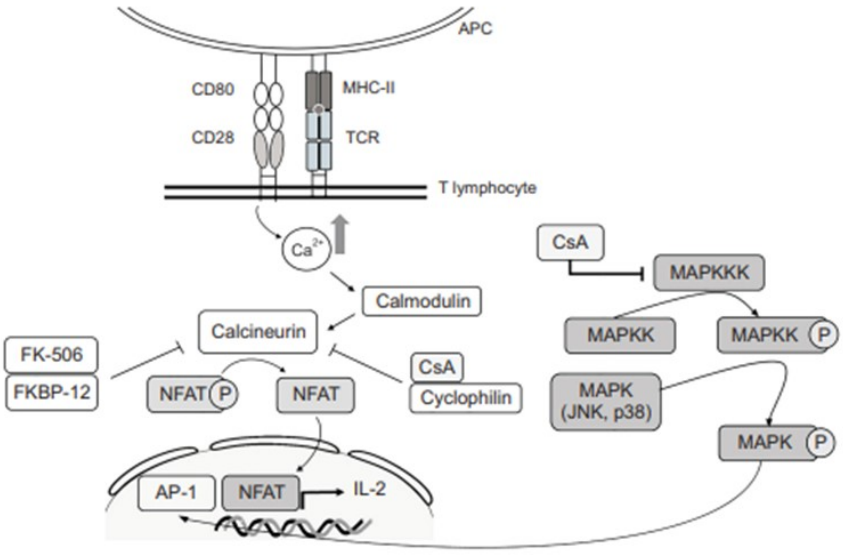

Figure 21. Mechanism of action of calcineurin inhibitors [71]

2.2.2. Cyclosporin A

Cyclosporin A (CsA) is a powerful immunosuppressive medication essential for preventing rejection of transplanted organs such as kidneys, livers, and hearts. CsA is derived from hydrophobic cyclic peptides of fungal origin, consisting of 11 amino acids, with 7 of these featuring N-methylated amide bonds. This structural composition enhances its stability in enzymatic degradation and in the different pH environments of the intestinal tract. [72, 73]

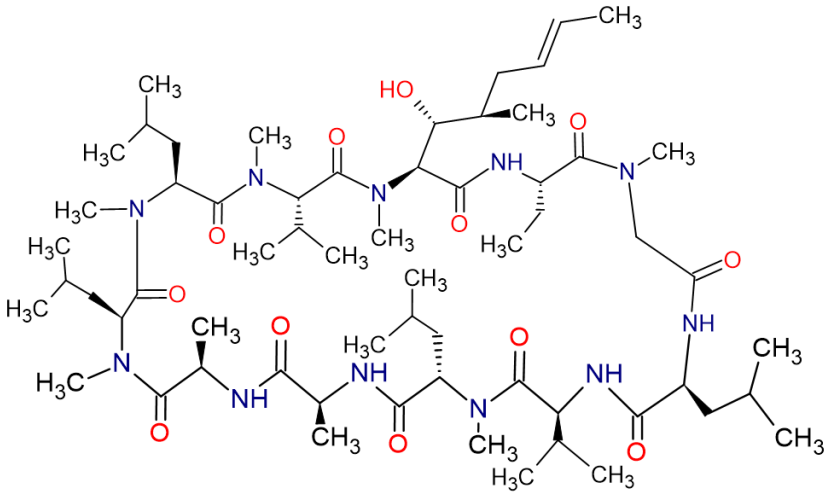

Figure 22. The chemical structure of cyclosporin A

Administration of CsA can be oral in capsule or liquid form, as well as intravenous. The liquid form necessitates dilution, preferably with orange or apple juice; however, grapefruit juice is contraindicated due to potential interaction risks. [72]

Following oral administration, CsA shows slow and incomplete absorption, typically between 20 % and 50 %, compared to almost complete absorption with intravenous infusion. After entering into the bloodstream, it rapidly distributes to tissues, organs and blood reservoirs. Significant proportion (95%) of CsA binds to plasma proteins and accumulates mainly in the liver, where it is metabolized by cytochrome P-450 enzymes, especifically via CYP3A4.The main route of excretion is via the bile (94%), with minimal excretion through the urine (6%) and only 0.1% as unchanged drug. [74]

Cyclosporine is a drug that frequently interacts with a large number of medications due to its metabolic profile. Parallel use with inducers of cytochrome p450 enzymes in the liver, such as anticonvulsants, rifampicin, preparations based on St. John's herb (hypericin as the active ingredient) and many others, induce an increment in the metabolism of cyclosporine and a

decline in its concentration in the blood. On the other hand, use in combination with CYP-3A enzyme inhibitors such as macrolides, antifungals, antidepressants, calcium channel blockers, and grapefruit juice increases the concentration of ciclosporin in the blood and could increase the risk of toxicity.

Therapy with ciclosporin requires careful monitoring of drug levels in the blood, because absorption and metabolism varies significantly and the therapeutic index is low. [72]

CsA plays a pivotal role in immunosuppressive therapy, crucial for transplant recipients and certain autoimmune conditions. However, its use mandates vigilant monitoring due to potential side effects and drug interactions.

2.2.3. Tacrolimus (Prograf, FK 506)

Tacrolimus, a neutral macrolide lactam containing a 23-membered lactone ring, was discovered in 1984 by Kino and colleagues during their search for molecules with immunosuppressive properties similar to cyclosporine. This compound was originally isolated from the fermentation broth of a Japanese soil sample containing the bacterium Streptomyces tsukubaensis. [75, 76]

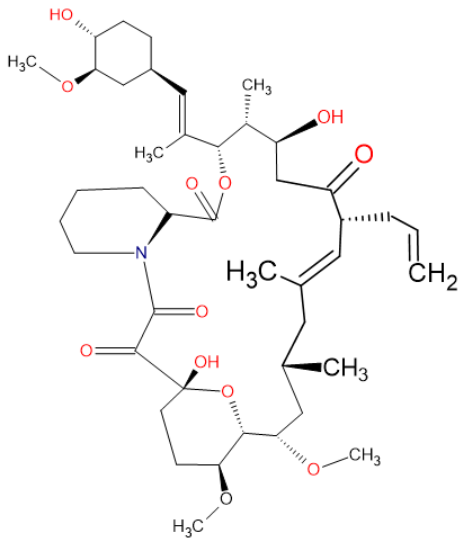

Figure 23. The chemical structure of tacrolimus

Initial laboratory tests and animal studies demonstrated that FK-506, later known as tacrolimus, exhibited strong immunosuppressive properties on both humoral immune response via Th2 lymphocytes and cellular immune responses via Th1 lymphocytes. The

mechanism of action is alike to that of cyclosporine, but tacrolimus is significantly more potent, exhibiting 10 to 100 times the efficacy at equivalent concentrations. Upon entering the cytoplasm, tacrolimus binds to the immunophilin FK506 binding protein (FK BP-12), forming a complex that more effectively inhibits the phosphatase activity of calcineurin compared to cyclosporine. [71]

In 1989, Starzl and colleagues published the results of the first clinical study of tacrolimus in liver transplant patients who had not responded to standard immunosuppressive therapy. They reported impressive outcomes, particularly noting the reduced side effects compared to cyclosporine. [75, 77]

Tacrolimus can be administered orally, sublingually, topically, or intravenously. Following oral administration, it undergoes significant first-pass metabolism in the liver, mediated by enzymes such as cytochrome P450 and P-glycoprotein (P-gp). The primary enzymes involved in the metabolism of tacrolimus are CYP3A4 and CYP3A5, with CYP3A5 being relevant only in individuals possessing at least one CYP3A5*1 allele.

Tacrolimus is well and constantly absorbed from the gastrointestinal tract and binds extensively to plasma proteins, allowing it to reach all organs except the brain, as it does not cross the blood-brain barrier. The drug is predominantly eliminated as metabolites via the bile, with less than 1% excreted unchanged in the urine. [78, 79]

Due to its narrow therapeutic index, careful monitoring of tacrolimus concentrations is essential. It is often used in combination with other drugs that are substrates of the CYP3A and P-gp enzymes, which can inhibit or induce tacrolimus metabolism. Consequently, close attention to dosing and monitoring is necessary to mitigate potential toxicity and ensure therapeutic efficacy. [79]

2.2.4. Application of cyclosporine and tacrolimus therapy in dental medicine

Cyclosporine and tacrolimus have shown significant benefits in dental medicine, particularly in the treatment of oral diseases associated with immunological disorders. A major area of application is the treatment of lichen planus (OLP), an illness characterized by inflammation of the oral mucosa.

The efficacy of ciclosporin in treating lichen planus is supported by clinical evidence. In one study, two patients with critical skin lichen planus received orally administered CsA at a

dosage of 6 mg/kg per day. This treatment led to complete resolution of symptoms, with the patients remaining free of the disease for 10 months. Similarly, in another case report, patients experienced significant improvement within two weeks of starting therapy, including reduced itching and cessation of new lesions. Existing lesions began to flatten by three to four weeks, and in period of eight weeks, both patients achieved complete remission. These findings underscore the effectiveness of ciclosporin in managing lichen planus, highlighting its potential as a therapeutic option for this condition. [80, 81]

Cyclosporine is also used to treat oral thrush, a common condition that causes painful ulcers on the oral mucosa. In addition, ciclosporin is being investigated as a potential therapy for the oral manifestations of autoimmune diseases such as lupus and pemphigoid. [82]

In addition to the established use of cyclosporine, studies have demonstrated the effectivness and safeness of topical tacrolimus in treating oral lichen planus. Topical tacrolimus is a valuable second-line treatment for OLP, particularly in cases that do not respond to potent topical corticosteroids. The treatment involves direct application to the affected areas, with the frequency and duration adjusted according to the severity of the condition and the patient's response. Long-term use of topical tacrolimus is generally safe, with minimal systemic absorption. However, some patients may experience local side effects, such as burning or irritation at the application site. [83]

2.2.5. Side effects of ciclosporin and tacrolimus therapy in the oral cavity

Cyclosporine frequently induces gingival hyperplasia, an exudative-proliferative inflammation that results in thickening and swelling of the interdental and marginal gingiva. This side effect occurs in approximately 30% of patients taking more than 500 mg daily and complicates the maintenance of adequate oral hygiene. The mechanism of cyclosporine-induced gingival hyperplasia involves increased production of extracellular matrix and collagen by gingival fibroblasts. This condition is typically more pronounced in the front teeth but does not occur in edentulous areas. The gingiva often appears dark red, has a granular surface, and is predisposed to bleeding.

Risk factors include dosage, genetic predisposition, patient oral hygiene, and the presence of plaque and calculus. Effective treatment methods begin with thorough plaque control through improved oral hygiene and professional removal of plaque. In some cases, cyclosporine

therapy can be replaced by tacrolimus, which is less toxic and causes less gingival overgrowth. [84]

Recently, the studies report that combination of azithromycin with cyclosporine is clinically effective in depletion of gingival hyperplasie and bleeding. This combination improves gingival hyperplasia without the need to change the medication. If these treatments are insufficient, necessary surgical interventions such as gingivoplasty, scalpel, laser, or electrosurgical gingivectomy, and flap surgery may be considered. [84, 85]

In addition to gingival hyperplasia, other side effects of cyclosporine have been observed, including hypertrophy of the filiform papillae on the tongue, opportunistic infections such as candidiasis, squamous cell carcinoma of the lips, non-Hodgkin lymphoma, and lymphoproliferative disorders in the oral cavity. [86]

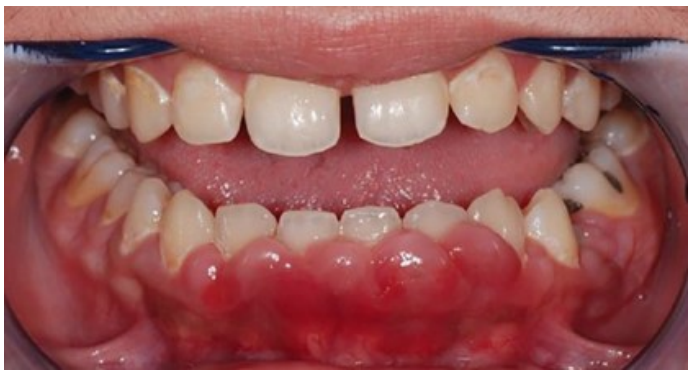

Figure 24. Gingival hyperplasia induced by cyclosporine [87]

Regarding the adverse effects of tacrolimus in the oral cavity, it is associated with the development of non-gingival exudative-fibrous soft tissue polyps known as pyogenic granuloma.

Pyogenic granuloma is a benign vascular tumor predominantly located in oral tissues. Its etiology is not fully clear, but it is believed to arise in response to various stimuli, including local irritation, traumatic injuries, hormonal influences, and certain medications. Clinically, pyogenic granulomas present as rapidly growing, smooth, soft, and red lesions. These lesions are composed of granulation tissue, inflammatory infiltrates, and exhibit significant angiogenic activity. They most commonly appear in the anterior maxillary region and the vestibular gingival zone (accounting for 75% of cases), but can also manifest on the lips, tongue, palate, or other oral mucosal sites. [88]

The size of pyogenic granuloma (PG) can differ from millimeters to centimeters. Depending from its age it varies in colour: younger PGs are more red due to a high density of vascular network, while older lesions look more pink. The consantcy of oral PGs also varies with the age of the lesion: as collagen fibers accumulate over time, the structure of the lesion gets stronger texture. [89]

Surgical removal is the preferred treatment modality for pyogenic granulomas. However, alternative approaches such as laser therapy, cryosurgery, or corticosteroid injections are also utilized. To prevent recurrence, it is essential to ensure accurate diagnosis, appropriate treatment, and the elimination of potential irritants. [88]

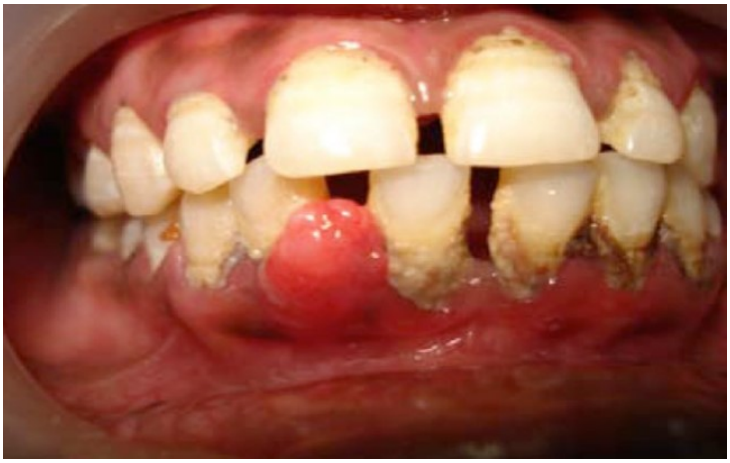

Figure 25. Pyogenic granuloma [90]

2.3. Inhibitors of nucleotide biosynthesis

Nucleotide biosynthesis inhibitors are pharmaceutical agents that block or slow down the production processes of nucleotides, the fundamental building blocks of nucleic acids in the body. Nucleotides are essential for various biological processes and are continuously anew produced in all cells. For DNA replication and RNA production an elevated nucleotide synthesis is aquired to support protein synthesis. This process is energy-intensive, utilizes various metabolic pathways and it is managed at the transcriptional level by major transcription factors, as well as at through feedback inhibion at the enzyme level.

Nucleotide biosynthesis inhibitors are used in medicine as therapeutic agents for the treatment of various diseases, including malignant tumors, autoimmune diseases such as psorias and rheumatoid arthritis, and infectious diseases like HIV/AIDS. Their mechanisms of action vary

depending on the specific target. Given the broad application and importance of these agents in medicine, ongoing research aims to develop more effective and selective therapies, reduce adverse effects, and improve clinical efficacy. [91]

2.3.1. Biosynthesis of pyrimidines

The biosynthesis of pyrimidines follows a de novo pathway involving several key steps. Initially, carbamoyl phosphate is formed from glutamine, ATP, and bicarbonate by the enzyme carbamoyl phosphate synthase (CPS). This compound is then transformed to carbamoyl aspartate through the action of aspartate transcarbamylase (ATC). In the next step, dihydroorotase (DHOase) converts carbamoyl aspartate to dihydroorotate.

Dihydroorotate is subsequently oxidized to orotate by dihydroorotate dehydrogenase (DHODH), a mitochondrial enzyme. Orotate is then transformed into orotidine monophosphate (OMP) by the enzyme orotate phosphoribosyltransferase, which utilizes PRPP in the process. Finally, OMP is converted to uridine monophosphate (UMP) by OMP decarboxylase.

UMP plays a central role in the synthesis of RNA and DNA. It can be phosphorylated to UDP by CMP kinase (CMPK), and UDP is further phosphorylated to UTP by nucleoside diphosphate kinase (NDPK). UTP can be converted to CTP by CTP synthase (CTPS).

For DNA synthesis, UDP is reduced to dUDP by ribonucleotide reductase (RNR). dUDP is then phosphorylated to dUTP by NDPK, converted to dUMP by dUTPase, and dUMP is converted to dTMP by thymidylate synthase (TS). Finally, dTMP is phosphorylated to dTDP and then to dTTP by corresponding kinases.

In addition to the de novo pathway, pyrimidine nucleotides can be recycled through the salvage pathway. Uridine and cytidine are key nucleosides in this process. Uridine is phosphorylated to UMP by uridine cytidine kinase (UCK), while cytidine can be deaminated to uridine by cytidine deaminase (CDA) or directly phosphorylated to CMP by UCK. CMP can then be phosphorylated to CDP and subsequently to CTP. Alternatively, CDP can be reduced to dCDP and phosphorylated to dCTP. [92]

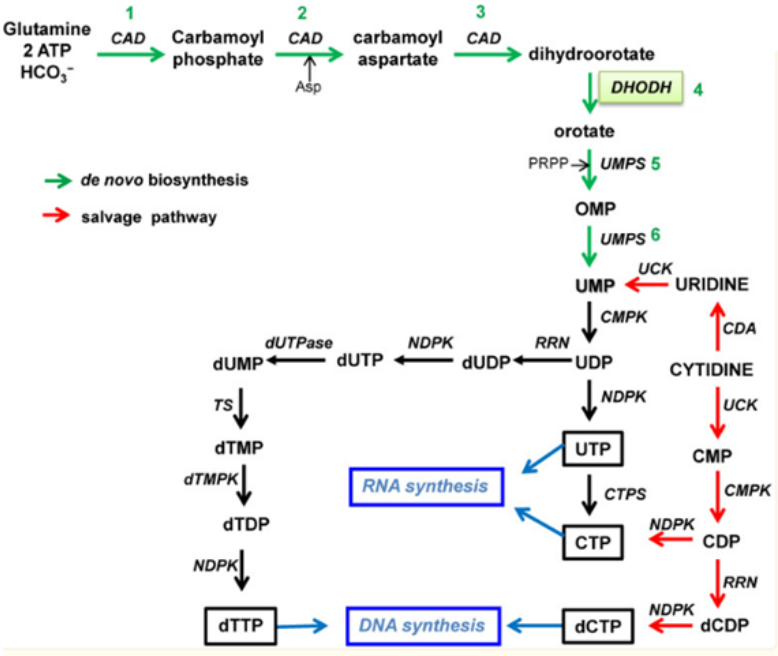

Figure 26. Pathways for Pyrimidine Nucleotide Synthesis: De Novo and Salvage Routes [92]

This comprehensive pathway ensures the synthesis of essential pyrimidine nucleotides, with UMP being a critical precursor for the production of other nucleotides necessary for nucleic acid synthesis. Understanding these processes is crucial for appreciating how cells meet their nucleotide requirements for various functions, including DNA and RNA synthesis.

2.3.2. Biosynthesis of purines

The biosynthesis of purines follows a complex de novo pathway involving ten steps to produce inosine monophosphate (IMP) from phosphoribosyl pyrophosphate (PRPP).

Initially, PRPP reacts with glutamine in a reaction catalyzed by phosphoribosylamidotransferase (PRAT) to form phosphoribosylamine (PRA).

PRA then reacts with glycine, catalyzed by GAR synthetase (GARS), to form glycinamide ribonucleotide (GAR). The enzyme GAR transformylase (GART) adds a formyl group from formyl tetrahydrofolate (Formyl-THF) to produce formylglycinamide ribonucleotide (FGAR).

Next, FGAR is converted to formylglycinamidine ribonucleotide (FGAM) by FGAM synthetase (FGAMS). FGAM undergoes cyclization by AIR synthetase (AIRS) to form aminoimidazole ribonucleotide (AIR). AIR is then carboxylated by AIR carboxylase (AIRC) to produce carboxyaminoimidazole ribonucleotide (CAIR). CAIR reacts with aspartate, catalyzed by SAICAR synthetase (SAICARS), to form succinylaminoimidazole carboxamide

ribonucleotide (SAICAR). Adenylosuccinate lyase (ASL) then eliminates fumarate from SAICAR to yield aminoimidazole carboxamide ribonucleotide (AICAR).

AICAR is converted to formylaminoimidazole carboxamide ribonucleotide (FAICAR) by AICAR transformylase (AICART), adding a formyl group from formyl-THF. Finally, IMP cyclohydrolase (IMPCH) assembles the intramolecular ring closure of FAICAR to produce inosine monophosphate (IMP), the key intermediate for purine nucleotide synthesis.

IMP serves as the precursor for the synthesis of other purine nucleotides. It is converted to adenylosuccinate (SAMP) by SAMP synthetase (SAMPS) and then to adenosine monophosphate (AMP) by adenylosuccinate lyase (SAMPL). Alternatively, IMP is oxidized to xanthosine monophosphate (XMP) by IMP dehydrogenase (IMPDH). XMP is then aminated to guanosine monophosphate (GMP) by GMP synthetase (GMPS). [92]

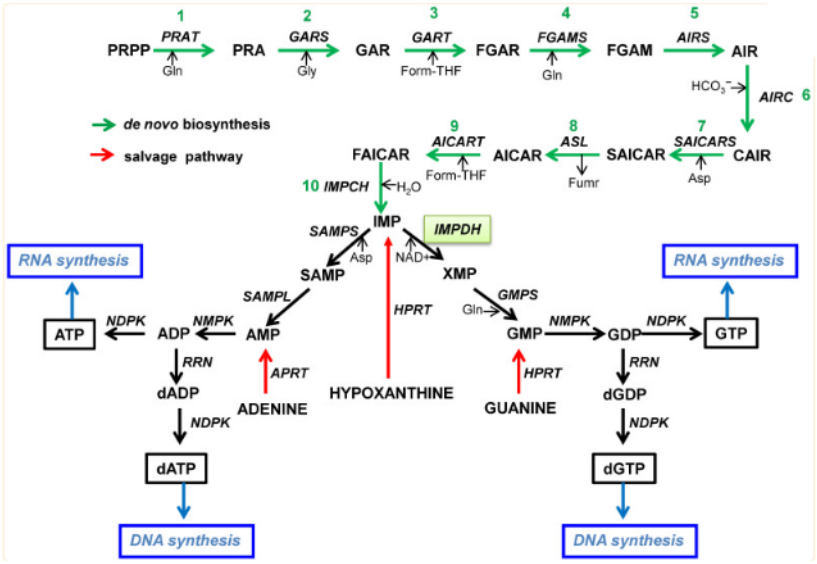

Figure 27. Pathways for Purine Nucleotide Synthesis: De Novo and Salvage Routes [92]

Purine nucleotides can also be synthesized via salvage pathways, where adenine, guanine, and hypoxanthine are recycled to their corresponding monophosphates by specific phosphoribosyltransferases (APRT and HPRT) using PRPP. AMP and GMP are then further phosphorylated to their respective diphosphates (ADP and GDP) and triphosphates (ATP and GTP) by nucleoside diphosphate kinase (NDPK).

For DNA synthesis, AMP is reduced to dAMP by ribonucleotide reductase (RNR), later subsequently phosphorylated to dATP by NDPK. Similarly, GMP is reduced to dGMP and then phosphorylated to dGTP. This comprehensive pathway ensures the supply of purine nucleotides necessary for various cellular functions, including RNA and DNA synthesis. [92]

Inhibiting pyrimidine and purine synthesis is crucial for treating various diseases, including cancer and autoimmune disorders. This strategy shows significant promise in dental medicine, particularly for managing oral cancers and viral infections in the oral cavity, as these conditions rely on rapid cell division and nucleic acid replication. Additionally, controlling nucleotide production can effectively regulate inflammatory responses and periodontal diseases by limiting the activity of proliferating immune cells. This approach highlights the potential for targeted therapies to enhance oral health and address systemic diseases with oral manifestations.

2.3.3. Azathioprine

Azathioprine, 6-mercaptopurine (6-MP), and 6-thioguanine (6-TG) are purine antimetabolites with immunosuppressive properties. The introduction of these thiopurine drugs as key agents in medical therapy marks a significant advancement in the treatment of an immense range of diseases, from autoimmune to malignant conditions. These drugs, particularly azathioprine, are synthetic analogs of natural purine bases and precursors of mercaptopurine. Their mechanism of action is based on the supression of purine metabolism and nucleic acid synthesis, significantly contributing to the reduction of certain cell populations, especially B and T lymphocytes, during inflammatory processes. [93]

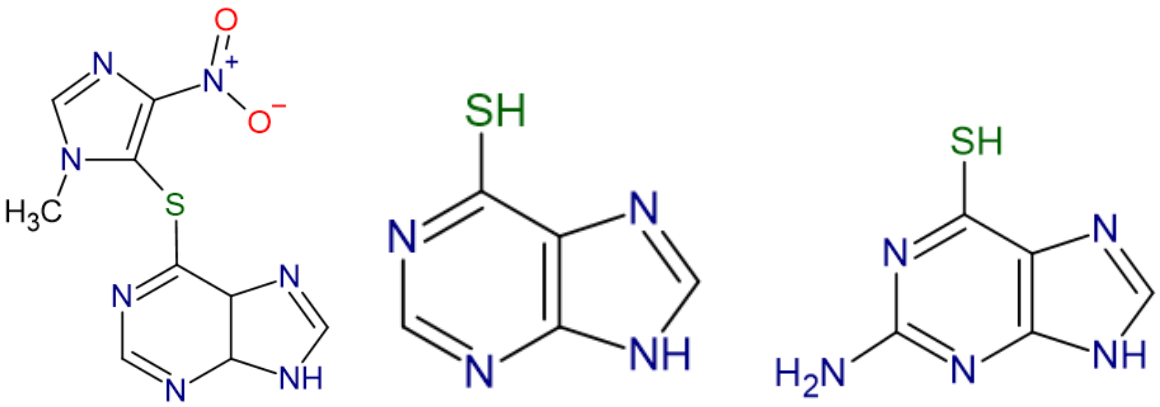

Figure 28. , 29. , and 30. The chemical structure of azathioprine, 6-mercaptopurine, and 6-thioguanine

Despite its effectiveness, azathioprine requires careful monitoring due to potential side effects and interactions with other medications. Understanding its mechanisms and clinical applications is crucial for optimizing patient outcomes in the treatment of autoimmune disorders.

Mechanism of action of Azathioprine (AZA)

Azathioprine (AZA) is a prodrug that is transformed to 6-mercaptopurine (6-MP) by glutathione transferases (GSTs) or non-enzymatically in the bloodstream. 6-MP is then transformed within cells into active substances known as thiopurine nucleotides, which are essential for its therapeutic effect. The balance between activation and deactivation of 6-MP in the bone marrow is crucial for its immunosuppressive action.

The first step in converting 6-MP into active substances is its transformation into 6-thioinosine monophosphate (6-TIMP) by the enzyme hypoxanthine phosphoribosyltransferase (HPRT). 6-TIMP is further converted into 6-thioguanosine monophosphate (6-TGMP), which then becomes 6-thioguanosine diphosphate (6-TGDP) and 6-thioguanosine triphosphate (6-TGTP). 6-thioguanine nucleotides (6-TGNs) incorporate into lymphocyte DNA, causing apoptosis of activated T-lymphocytes and pushing cytotoxic effects at higher doses. Additionally, 6-TGTP, a form of 6-TGN, inhibits the activity of GTPase Rac1, thereby suppressing T cell-dependent immune responses. 6-MP and 6-thioguanine are eliminated through biotransformation into inactive metabolites. 6-MP is catabolized by xanthine oxidase (XO) into thiouric acid, the main catabolite present in urine. [93]

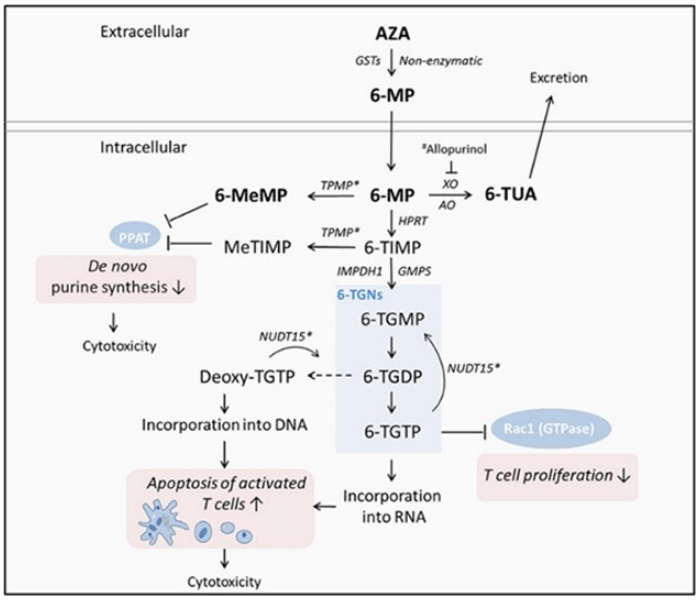

Figure 31. Simplified metabolism of thiopurines and mechanisms of action [93]

Another possible pathway is converting 6-MP to 6-methylmercaptopurine (6-MeMP) or methylthioinosine monophosphate (meTIMP) by thiopurine methyltransferase (TPMT). These metabolites inhibit the enzyme PPAT, reducing de novo purine synthesis, DNA synthesis, cell proliferation, and causing cytotoxic effects.

Genetic polymorphisms in enzymes like TPMT significantly affect thiopurine metabolism. Patients with TPMT deficiency (complete or partial) are at risk for severe myelosuppression when treated with basic doses of AZA or 6-MP. Approximately 10% of Caucasians are heterozygous for a TPMT allele, and 0.3–0.5% are homozygous. Patients with TPMT deficiency should receive reduced thiopurine doses to avoid toxicity.

Conversely, overexpression of TPMT leads to thiopurine hypermethylation, linked to not responding to treatment and toxicity of the drug. Co-therapy with allopurinol, which inhibits xanthine oxidase, can improve 6-TGN production, promoting clinical remission.

Additionally, NUDT15 gene variants impact thiopurine metabolism. The enzyme NUDT15 dephosphorylates TGTP and deoxyTGTP, preventing their DNA incorporation. Reduced NUDT15 activity results in higher levels of active 6-TGNs, leading to myelotoxicity and necessitating lower thiopurine doses. [93]

In summary, azathioprine (AZA) is transformed into 6-mercaptopurine (6-MP) in the body. 6-MP is then metabolized into various active substances that either get incorporated into the DNA and RNA of immune cells, leading to cell death and reduced cell proliferation, or inhibit the synthesis of purines. These actions collectively suppress the immune system, making azathioprine effective in treating conditions involving an overactive immune response.

Application of azathioprine

Azathioprine stands out as a potent immunosuppressive agent, used in the therapy of autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, and inflammatory bowel diseases. It is also applied in the prevention of transplant rejection following organ transplantation. Additionally, this drug may be beneficial in the treatment of infectious diseases, including viral infections such as HIV/AIDS.

Lupus Erythematosus

Lupus erythematosus is a lifelong, inflammatory, autoimmune, multisystemic disease that predominantly alters the skin. It encompasses a wide spectrum of clinical forms, with symptoms ranging from mild skin manifestations to severe organ damage. The disease presents in various forms depending on the severity of the clinical picture and the extent of organ involvement.

The most common forms are Discoid Lupus Erythematosus (DLE) and Systemic Lupus Erythematosus (SLE).

Even though the exact reason of lupus erythematosus is undiscovered, it is believed that genetic predisposition and environmental factors significantly contribute to the disease's onset. These factors include infections, particularly those caused by the Epstein-Barr virus, hormonal imbalances, exposure to ultraviolet light, smoking, strict diets, and the use of certain medications. [94]

Discoid Lupus Erythematosus

Discoid lupus erythematosus is a more prevalent form of the disease. It is defined by changes in the skin, eyes and oral mucosa. The skin presents with scaly, erythematous patches that are clearly demarcated from clinically healthy skin. As the disease progresses, these erythematous patches may develop into areas of skin atrophy with hypo- or hyperpigmentation. The most frequent locations are sun-exposed areas, particularly the head and neck. Patients often report that these skin changes worsen with sun exposure.

On the face, especially in the nose and cheek regions, the lesions appear in a butterfly-shaped distribution. These changes are symmetrical. Over time, these lesions may heal spontaneously but can reappear in different areas, persisting for months. In the eyes, lupus can cause cicatricial conjunctivitis, eventually leading to vision impairment.

The oral mucosa is affected in 15-25% of patients, often accompanying skin changes. However, in rare cases, lesions in the oral mucosa may occur independently, without skin involvement. Typical lesions in the oral mucosa are characterized by pronounced atrophy or ulceration on an erythematous surface, sharply demarcated, with a raised edge from which dilated blood vessels radiate in striae. Telangiectasia may also be observed. The buccal mucosa, lower lip, palate, gingiva, and tongue are most commonly affected. [95]

The clinical characteristics of oral lesions are not pathognomonic for this disease and can sometimes be difficult to identify.

Systemic Lupus Erythematosus (SLE)

Systemic lupus erythematosus is a severe disease that affects mucous membranes, cardiovascular and gastrointestinal systems, skin, kidneys, lungs and nervous system. This condition is followed by fatigue, fever, weight loss, arthritis, exhaustion, and other symptoms.

Most patients experience musculoskeletal symptoms such as arthralgia (joint pain) and brief morning joint stiffness.

Characteristic skin manifestations occur in 40-50% of patients, including a butterfly-shaped erythematous rash on the face and erythematous or maculopapular rashes affecting broader sun-exposed areas of the skin. Other skin symptoms may include purpura, subacute nodules, alopecia, vitiligo, or hyperpigmentation.

Pulmonary function abnormalities are common, including dry or exudative pleuritis. The kidneys are affected in approximately 40-50% of cases, which can progress to glomerulonephritis and renal insufficiency over time. Cardiac involvement is also significant, with occurrences of pericarditis and heart valve damage due to verrucous vegetations.

Pathological changes in the oral mucosa occur in about 30-45% of patients. Oral mucosal lesions in systemic lupus erythematosus are not pathognomonic. Clinically, they present as large, painful erosions surrounded by a red or whitish zone, clearly demarcated from the surrounding tissue. Isolated enanthematous areas are also common, especially on the palate. Other frequent clinical findings include petechiae, edema, candidiasis, periodontal disease, dysgeusia, and xerostomia. As with discoid lupus erythematosus the most commonly affected regions are the palate, buccal mucosa and lips. [96]

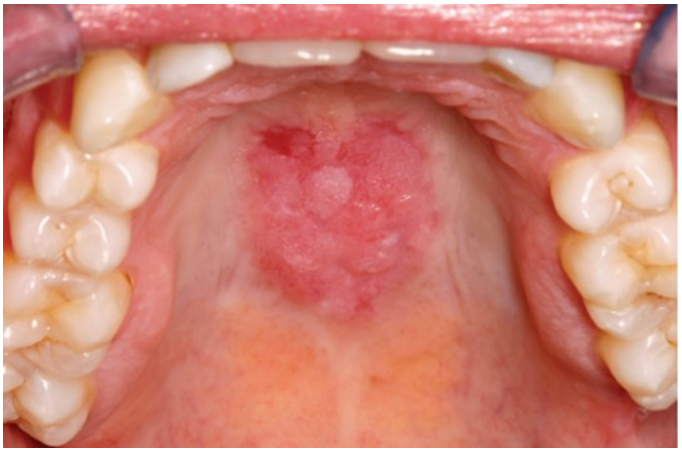

Figure 32. Red and white lesions on the hard palate in a patient with discoid lupus erythematosus [97]

Establishing a definitive diagnosis requires not only anamnesis and clinical findings but also histopathological examination, immunofluorescence testing, and laboratory results. Direct immunofluorescence staining for immunoglobulins IgM, IgG, and complement C3 shows their deposition along the basement membrane. Anemia, leukopenia, and thrombocytopenia are

common manifestations of systemic lupus erythematosus. Antinuclear antibodies (ANA) are present in 98% of patients; however, the ANA test is not specific to systemic lupus erythematosus and can also indicate other autoimmune diseases. Particularly specific to systemic lupus are anti-double-stranded DNA antibodies (anti-dsDNA), which are positive in about 60% of patients. For a correct diagnosis of systemic lupus erythematosus, a patient must meet at least 4 of the 11 established criteria at any point during the disease course.

Differential Diagnosis: Differential diagnosis consists of erosive lichen planus, erythema multiforme, leukoplakia, and dermatomyositis.

Therapy typically begins with corticosteroids, which are highly effective for controlling acute flares due to their potent anti-inflammatory effects. Antimalarial drugs, particularly hydroxychloroquine, also play a crucial role in the treatment of SLE. Hydroxychloroquine has immunomodulatory effects that help reduce the frequency of disease flares and improve long-term survival.

For patients requiring more intensive immunosuppression, drugs like azathioprine (AZA) are used. Azathioprine acts as a steroid-sparing agent, allowing for lower doses of corticosteroids and thereby reducing their side effects. It is particularly effective in maintaining remission and preventing severe complications such as lupus nephritis and central nervous system involvement. Other immunosuppressive agents include methotrexate, often used for severe arthritis and skin disease, and mycophenolate mofetil, which is especially effective in treating lupus nephritis. Cyclophosphamide is reserved for the most severe cases with significant organ involvement.

In recent years, biologic therapies have emerged as valuable additions to the SLE treatment arsenal. Belimumab, an anti-BLyS antibody, has demonstrated efficacy in reducing disease activity in patients who do not respond adequately to traditional therapies. [98]

Overall, the management of SLE involves a combination of medications to control disease activity and prevent flares, alongside lifestyle adjustments to improve patient outcomes and quality of life.

Side effects of azathioprine

The use of thiopurine drugs can be challenging due to their narrow therapeutic index, which can lead to serious toxic effects such as bone marrow suppression, leukopenia, thrombocytopenia, anemia, hepatitis, cholestasis, alopecia, infections, and malignancies.

Monitoring complete blood counts, testing TPMT enzyme activity before initiating therapy, assessing liver function, and tracking metabolite levels are essential during the administration of these drugs. [99]

Sidee effects of azathioprine in dentistry are a significant concern. AZA can cause taste disturbances such as ageusia, hypogeusia, and dysgeusia. One potential side effect is gingival hyperplasia, which is an overgrowth of gum tissue that can lead to discomfort and difficulty maintaining oral hygiene. Immunosuppression increases the risk of oral infections, including candidiasis and bacterial infections. Mucositis, which manifests as inflammation of the oral mucosa, can also occur with azathioprine therapy, causing pain and difficulty swallowing. Another possible effect is accelerated tooth loss, as well as hemorrhagic stomatitis, a condition characterized by bleeding from the oral mucosa. [100]

2.3.4. Cyclophosphamide

Cyclophosphamide, an alkylating agent from the oxazaphosphorine group, has been used for over 40 years in cancer treatment and to suppress immune responses in autoimmune diseases. Its immunosuppressive properties are crucial in transplantation medicine, where it is administered pre-transplant to restrain graft rejection and graft-versus-host disease. [101]

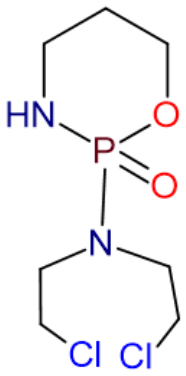

Figure 33. The chemical structure of cyclophosphamide

The drug effectively depletes T and B lymphocytes, thereby suppressing antibody production. Its mechanism involves alkyl groups inducing chromosomal damage, leading to abnormal or inhibited cell mitosis. Combining cyclophosphamide with other immunomodulatory drugs holds promise for advanced cancer treatment. [102]

The pharmacokinetics of cyclophosphamide is well absorbed orally, achieving plasma concentrations comparable to intravenous administration. It is primarily excreted via the kidneys, crosses the blood-brain barrier, and can be detected in cerebrospinal fluid. Additionally, it can be excreted in breast milk, necessitating caution in lactating patients.

However, therapeutic use of alkylating agents like cyclophosphamide is associated with significant toxicity, as therapeutic doses approach toxic levels. Careful consideration is required in selecting the appropriate preparation, type, and method of administration to balance efficacy and safety. [103]

Mechanism of action of cyclophosphamide

Cyclophosphamide is a nitrogen mustard drug that works by alkylating DNA, which means it adds alkyl groups to DNA molecules. This action is not specific to any cell cycle phase and through DNA and RNA crosslinking it blocks protein synthesis.

The drug's primary antineoplastic (anti-cancer) effects are result of a metabolite called phosphoramide mustard, produced when liver enzymes like cytochrome P-450 metabolize cyclophosphamide. This process involves converting cyclophosphamide to hydroxycyclophosphamide, then to aldophosphamide, which is further broken down into phosphoramide mustard and acrolein. Phosphoramide mustard creates cross-linkages in DNA, leading to cell death. Acrolein, although not anti-tumor, can cause hemorrhagic cystitis.

Apart from its anti-cancer properties, cyclophosphamide has immunosuppressive effects, particularly on T cells. High doses are used to eradicate malignant hematopoietic cells, while lower doses help modulate immune responses, decreasing certain inflammatory cytokines and increasing others. These properties make it useful in tumor vaccination protocols, managing post-transplant reactions, and treating immune-mediated conditions and some vasculitis forms. [103]

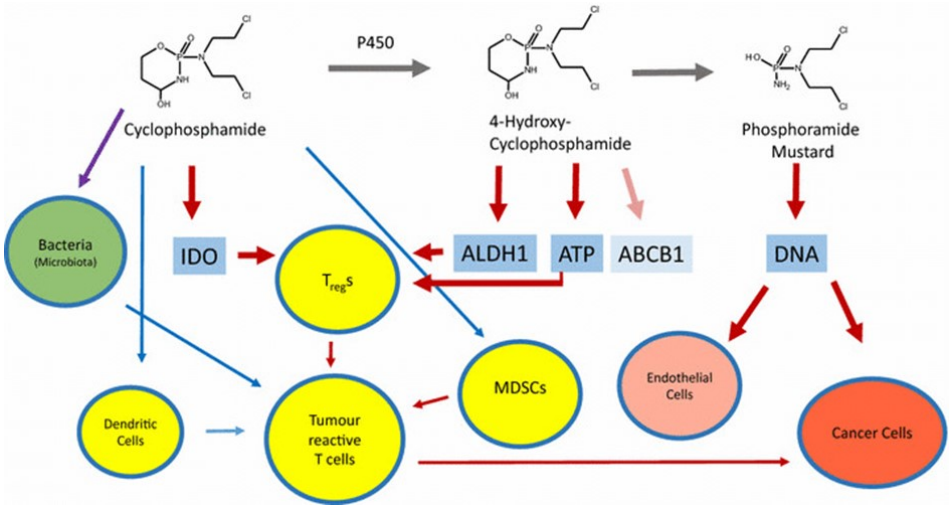

Figure 34. Mechanism of action of cyclophosphamide and its active metabolites on immune response [103]

Although the exact mechanisms of its immunomodulatory effects are not fully understood, studies suggest cyclophosphamide may dispose regulatory T cells, promote T cell growth factors, and prepare host cells for donor T cells, thus reducing immune rejection. [103]

Application of cyclophosphamide

Cyclophosphamide, a key agent in oncology and immunosuppression, demonstrates a broad spectrum of therapeutic applications. It is used extensively in treating various cancers such as breast, lung, esophageal cancers, among others, making it indispensable in combating malignant tumors. Approved by the FDA (Food and drug administration), cyclophosphamide is indicated for stages III and IV malignant lymphomas according to the Ann Arbor staging system, including Hodgkin's and Non-Hodgkin's lymphoma, Burkitt's lymphoma, lymphocytic lymphoma and multiple myeloma, highlighting its crucial role in oncology.

Additionally, it is recognized as an effective immunosuppressive agent in tissue and organ transplantation, preventing graft rejection and reducing complications like graft-versus-host disease.

Cyclophosphamide also plays a significant role in managing severe exacerbations of systemic lupus erythematosus (SLE) and other systemic diseases such as Wegener's granulomatosis. [103]

Granulomatosis with Polyangiitis

Granulomatosis with Polyangiitis (GPA), formerly known as Wegener's granulomatosis, is an unusal and possibly life-threatening systemic autoimmune disease defined by inflammation of small to medium-sized blood vessels. This condition, mediated by the immune system, often presents with periods of remission and relapse.

Initially described by Klinger in 1931 and later by Wegener in 1936, GPA is diagnosed grounded on criteria formed by the American College of Rheumatology. Criteria include ulcerative lesions on the oral mucosa or nasal bleeding, radiographic evidence of lung nodules or infiltrates, abnormal urinary sediment, and granulomatous inflammation on biopsy. [104]

GPA is characterized by three key pathological features: necrosis, granulomatous inflammation, and vasculitis. Necrosis is marked by irregularly distributed necrotic areas surrounded by multinucleated giant cells. Granulomatous inflammation involves macrophages and multinucleated giant cells, while vasculitis is characterized by fibrinoid necrosis and inflammatory infiltration of the vessel walls. [104, 105]

The exact cause of GPA remains unknown, but it is associated with anti-neutrophil cytoplasmic antibodies (ANCAs), particularly those targeting proteinase 3 (PR3) and myeloperoxidase (MPO). These antibodies activate neutrophils, leading to vascular damage and vasculitis. Environmental factors and infections, such as Staphylococcus aureus and Cytomegalovirus, may also trigger GPA in some individuals. [104]

Diagnosis of GPA is challenging due to its insidious onset, often resulting in an average delay of 4.7 to 15 months from symptom onset to diagnosis. Testing for ANCAs, particularly cytoplasmic ANCA (c-ANCA), is crucial, as c-ANCA is present in approximately 80% to 90% of GPA patients. Most c-ANCA-positive patients have antibodies directed against PR3, while those with a perinuclear ANCA (p-ANCA) pattern typically target MPO. [104, 105]

GPA typically begins as a localized process that, if untreated, can rapidly progress to involve multiple tissues or organs. The disease primarily affects the upper and lower respiratory tracts and kidneys, but can also involve the skin, central nervous system, heart, eyes, and gastrointestinal tract. Initial symptoms include fever, fatigue, sinusitis, nasal and oral ulcers, joint pain, and neurological issues. [105]

Oral lesions in GPA often present as nonspecific erosive or ulcerative lesions or as hyperplastic gingivitis. A distinctive feature is "strawberry gingivitis," characterized by enlarged, erythematous interdental papillae with red to purple petechiae and a granular appearance. [104, 105]

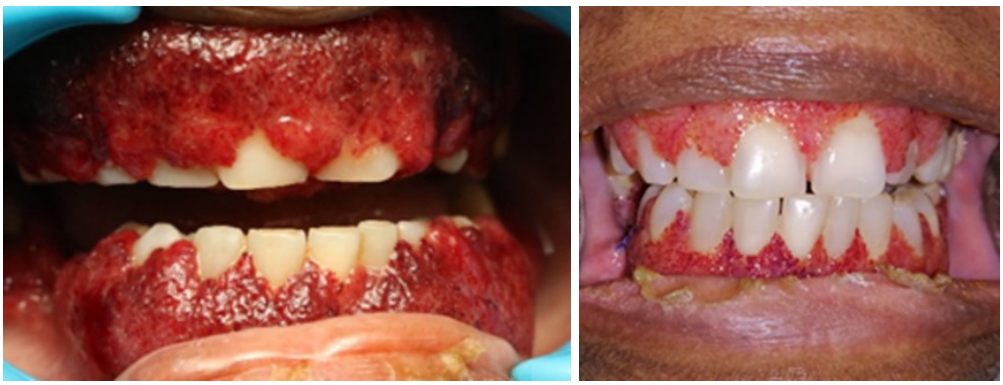

Figure 35. and 36. Granulomatosis with Polyangiitis [105]

Therapy for GPA is systemic and depends on disease severity and localization. Cyclophosphamide, combined with corticosteroids, is the mainstay treatment for severe cases, targeting immune suppression and inflammation control. Other drugs, such as azathioprine, methotrexate, rituximab, and corticosteroids, can be used depending on activity of the disease and patient response. Early diagnosis and aggressive treatment are crucial for managing GPA and improving patient outcomes.

Dental management of GPA patients focuses on infection prevention and management due to immunosuppressive therapy. Dental treatment should ideally precede the initiation of immunosuppressive therapy to minimize infection risks. During acute phases, only emergency dental procedures are recommended, with careful monitoring and consultation with the treating physician. Antibacterial mouthwashes and prophylactic antibiotics are prescribed before invasive dental procedures. [104]

In summary, GPA is a complex autoimmune vasculitis requiring prompt diagnosis and aggressive treatment to prevent organ damage. Dental management must prioritize infection control and patient safety, adhering to specific protocols tailored to the immunosuppressed state of GPA patients.

Side effects of Cyclophosphamide

Cyclophosphamide is associated with several significant adverse side effects. These include bladder toxicity, such as hemorrhagic cystitis, which can range from mild to severe bleeding, and other urinary symptoms like increased frequency, urgency, nocturia, and dysuria. Gonadal toxicity is also a concern, with potential irreversible infertility.

Myelosuppression caused by cyclophosphamide can lead to severe complications like sepsis and septic shock, requiring close monitoring and antibiotic therapy. Other serious side effects include cardiotoxicity, pulmonary toxicity, veno-occlusive liver disease, and an increased risk of secondary malignancies.

Prevelance of these side effects and increased mortality are connected to higher usage of cyclophospamide.

Preventive measures, such as adequate hydration, continuous bladder irrigation, and the use of mesna, are recommended to mitigate some of these risks. [103]

2.4. Biological agents

Biological agents represent a pivotal group of drugs in modern medicine, increasingly recognized for their therapeutic efficacy across various diseases. Distinguished from conventional pharmaceuticals, these agents are produced using biotechnological methods involving living organisms such as human and animal cells, yeasts, plants, and microorganisms.

The development of biological agents began decades ago but has accelerated with advances in recombinant technology. This technology enables the production of recombinant proteins by introducing human lymphoid cells into animals, followed by collection and purification of resulting antibodies. Biotechnological progress has facilitated the creation of high-quality polyclonal and monoclonal antibodies, which possess immunosuppressive properties by lysing lymphocytes and blocking their surface receptors that are developed to modulate different components of the immune system.

Their application is increasingly prominent in treating numerous diseases, including rheumatological disorders, tumors, diabetes, and autoimmune conditions. In recent years, the

number of approved biological drugs has significantly risen, establishing these agents as pivotal factors in both the pharmaceutical industry and medical practice. [106]

2.4.1. Some of the representatives of biological agents:

Humanized Anti-CD20 Monoclonal Antibody- Rituximab

Recent advancements in understanding autoimmune diseases have led to the development of more targeted immunosuppressive treatments.

Rituximab, a chimeric humanized monoclonal antibody of the IgG1 type, targets the CD20 antigen located exclusively on the B lymphocytes surface. It comprises a human constant (Fc) region and a murine variable (Fv) region, providing optimal pharmacokinetic properties. CD20 is a good target for therapy because it does not circulate freely in the blood, nor is it shed or internalized. Importantly, CD20 is absent on stem cells, early lymphoblasts, and mature plasma cells. [107]

Rituximab eliminates CD20-positive cells through several mechanisms, including antibody-dependent cellular cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), induction of apoptosis, and enhancement of the cytotoxic activity of certain drugs and radiotherapy. [108]

The use of rituximab is expanding worlwide, with an increasing range of clinical indications, particularly in dental medicine. Rituximab is approved for treating pemphigus vulgaris, and other autoimmune disorders that include granulomatosis with polyangiitis, systemic lupus erythematosus, and rheumatoid arthritis, as well as B cell malignancies, like non-Hodgkin's lymphoma (NHL) and chronic lymphocytic leukaemia. [109]

Systemic corticosteroids have traditionally been the cornerstone of pemphigus vulgaris (PV) treatment, achieving disease control within several weeks. However, the disappointing safety profile of chronic high-dose corticosteroid treatment has led to treatment regimens that combine corticosteroids with immunosuppressive agents, thereby reducing corticosteroid-related adverse effects. [110]

This summary emphasizes the effectivness and harmlessness of rituximab combined with a reduced number of corticosteroids for treating adults with moderate to severe pemphigus vulgaris.

Studies have shown that rituximab combined with short-term corticosteroids is significantly more effective and safer than corticosteroids alone. A higher proportion of patients on rituximab plus short-term, low-dose corticosteroids accomplished complete remission (CR) and successfully decreased the usage of corticosteroids for at least 2 and 3 months by month 24, compared to those on high-dose, long-term corticosteroids.

Rituximab was well-tolerated and demonstrated a steroid-sparing effect. Fewer severe corticosteroid-related adverse events took place in the rituximab plus prednisone group in comparison to the prednisone-alone group. There were not any new risks detected, and rituximab's safety profile was consistent with its use in other autoimmune conditions. [110]

Furthermore, research has shown that rituximab can help reduce periodontal inflammation and improve the overall condition of patients with periodontitis, presenting a new potential therapeutic approach in dental practice. [111]

Monoclonal antibody to TNF-α

Anti-TNF agents are biological medications that mitigate mucosal inflammation by blocking tumor necrosis factor-alpha (TNF). These drugs are typically the first choice in biologic therapy. Initially believed to work by directly neutralizing the pro-inflammatory cytokine TNF, recent studies indicate that TNF inhibitors may act through more complex mechanisms than simple inhibition.

Infliximab, a chimeric IgG1 monoclonal antibody binding to TNF, was introduced into clinical practice in the late 1990s as the first biologic therapy for inflammatory conditions.

The use of infliximab has shown promise for treating refractory oropharyngolaryngeal ulcers (ROUs) that are unresponsive to conventional treatments such as prednisolone. In a reported case, a patient with recurrent ROUs that did not respond to prednisolone was successfully treated with infliximab. The patient did not exhibit any symptoms of systemic diseases such as Behçet disease or inflammatory bowel disease (IBD).

Infliximab demonstrated rapid efficacy in this case. The patient's fifth ulcer, which occurred on the tongue, began to resolve after the third dose of infliximab, administered alongside prednisolone. Over the course of 17 months of treatment with infliximab administered every 8 weeks, no further ulcers appeared. This suggests that infliximab may be effective in preventing the recurrence of ROUs. [112]

The text highlights the potential of considering infliximab for treating refractory oral ulcers even in the absence of a confirmed systemic disease. Additionally, it suggests the importance of monitoring infliximab trough concentrations and antibodies to infliximab (ATI) to improve treatment outcomes.

However, the optimal treatment schedule for infliximab, including decisions about single-dose versus repeated administrations and the duration of treatment, remains unresolved. Further large randomized studies are necessary to determine safe and effective dosages, the ideal duration of treatment, and the role of infliximab in combination with other immunosuppressive agents for treating ROUs. Accumulating such data is crucial in establishing clinical criteria, understand the pathogenesis, as well as development of treatment guidelines for patients with refractory oropharyngolaryngeal ulcers. [112]

Infliximab can generate side effects, most of which are not dangerous. Common side effects include mild respiratory infections, headaches, rash, and gastrointestinal disturbances. Because infliximab affects the immune system, it can increase susceptibility to infections. There is also a risk of allergic reactions to the intravenous infusion, particularly if the treatment pause exceeds 16 weeks. [113]

Adalimumab is the first fully human monoclonal antibody of the IgG1 class that targets tumor necrosis factor-alpha (TNF-α). This biologic agent is utilized in the treatment of various chronic inflammatory conditions, including rheumatoid arthritis, , ankylosing spondylitis, psoriatic arthritis, Crohn's disease, chronic psoriasis, ulcerative colitis, and juvenile idiopathic arthritis. This antibody exerts its therapeutic effects by binding to both soluble and membrane-bound TNF-α, thereby inhibiting its interlinkage with the p55 and p75 cell surface receptors. This interaction blockade prevents the downstream inflammatory signaling pathways typically mediated by TNF-α.

The mechanism of action of adalimumab involves the destruction of cells expressing TNF-α in the presence of complement. Additionally, it effectively reduces the concentration of inflammatory cytokines, such as interleukin-6 (IL-6), C-reactive protein (CRP), and erythrocyte sedimentation rate (ESR), all of which are markers indicative of inflammatory processes. Adalimumab is administered via subcutaneous injection, and it has an elimination half-life ranging from 10 to 20 days, allowing for convenient dosing schedules. [114]

Recent studies have highlighted the positive effects of adalimumab, an anti-TNF-α agent, in the management of various oral and dental conditions. Originally developed for treating

systemic chronic inflammatory diseases, adalimumab has shown promising results in specific conditions within the oral cavity. Notable findings include:

Oral Lichen Planus: A pilot study has demonstrated that adalimumab can effectively manage symptoms of oral lichen planus, an inflammatory condition characterized by painful lesions in the mouth. Patients receiving adalimumab treatment exhibited significant improvements in lesion size and pain reduction, suggesting its potential as a therapeutic option for this condition. [115]

Behçet's Disease: Adalimumab has been used off-label to treat severe oral ulcers in patients with Behçet's disease. Clinical outcomes have shown rapid healing of ulcers and prolonged remission periods in several cases, indicating that adalimumab may be a valuable therapeutic option for managing severe oral manifestations of this disease. [116]

Periodontal Disease: In cases of severe periodontitis, adalimumab has been observed to reduce inflammation and improve periodontal health. These findings recommend a potential role for adalimumab in the management of periodontal diseases that are resistant to conventional therapies. [115]

The use of adalimumab in dental medicine and for treating conditions in the oral cavity is promising, particularly for patients with refractory or severe inflammatory conditions. However, extensive clinical trials are necessary to establish standardized treatment protocols and to determine the long-term efficacy and safety profiles of adalimumab for these specific uses.

Adalimumab is suitable for long-term and continuous use, with a minimal risk of rebound effect upon discontinuation. To mitigate the risk of antibody formation against adalimumab, it is often combined with methotrexate. In pregnancy, adalimumab is categorized as a category B drug. Common side effects include pain at the injection site, while more serious complications can involve malignancies, severe infections (including tuberculosis), and cytopenias. Due to the risk of tuberculosis, periodic testing for tuberculosis and monitoring of liver enzymes are recommended. [114]

In conclusion, adalimumab represents a significant advancement in the treatment of chronic inflammatory diseases, with emerging applications in oral and dental conditions. Further research is warranted to fully elucidate its potential in these new therapeutic areas and to ensure its safety and efficacy in long-term use.

2.4.2. Specific Applications in dentistry

Orofacial Pain

Orofacial pain is a prevalent health issue that significantly impacts daily activities, with many cases linked to dental conditions. The causes can be classified as oral or extraoral. [117]

Oral causes of orofacial pain include dental caries, which, if untreated, can progress to pulpitis (inflammation of the dental pulp) and dentine hypersensitivity, characterized by short, sharp pain in response to stimuli without a recognizable organic cause. These issues are directly related to the teeth and structures within the mouth.

Extraoral causes include temporomandibular disorders (issues with the jaw joint), neuralgias (such as trigeminal neuralgia), myofascial pain (pain in the facial and jaw muscles), sinusitis (inflammation of the sinuses that can cause facial pain), and vascular pain associated with migraines or cluster headaches. These causes originate outside the oral cavity and can lead to pain in the face and jaw area.

The sensory system and innervation within the orofacial region are complex, complicating the understanding of nociceptive signal transduction and pain treatment. This complexity can result in inadequate treatment, overtreatment, or inappropriate management of dental pain. Misinterpretation of pain origin, as highlighted by Pigg and colleagues, can lead to misdiagnosis and poor management, a significant issue in dentistry where pain is a common adverse event. [118, 119]

Standard treatments typically involve the use of analgesics and sedatives. However, the use of biological agents represents a significant advancement in the treatment of orofacial pain, particularly when associated with systemic inflammatory or autoimmune conditions. These therapies provide targeted intervention, addressing the root causes of inflammation and offering relief from chronic pain.

One approach involves the continuous production and secretion of proteins that reduce pain sensation in or around the spinal cord. This can be achieved in two ways: through vector integration, such as adeno-associated virus (AAV), or a therapeutic protein-plasmid encapsulated in lipids that encode interleukin-10 (IL-10), injected into the subarachnoid space to transduce cells. Another approach uses a modified herpes virus delivered to the nerves of the dorsal root ganglion through intradermal injection. The herpes virus is utilized for its ability

to infect nerve fibers and reach the dorsal root ganglion through nerve endings in the skin. In the dorsal root ganglion, the virus can encode an inhibitory neurotransmitter, an anti-inflammatory peptide, or reduce the synthesis of endogenous molecules that cause pain, leading to symptom relief. [118]

Proper diagnosis and management of orofacial pain require careful attention to the patient's symptoms. This review aims to summarize the characteristics of sudden and persistent orofacial pain, focusing on therapy of neuropathic pain. Additionally, it emphasizes the importance of accurate diagnosis and differential diagnosis between neuropathic and neuralgic pain to guide effective dental treatment. [117]

Neuropathic pain is induced by injury or dysfunction in the nervous system, affecting either peripheral or central pathways. This type of pain is often described as burning, tingling, or shooting and can result from conditions such as diabetes, shingles, or nerve injuries. Pathophysiologically, neuropathic pain involves abnormal nerve signaling due to demyelination, axonal damage, or altered neurotransmitter release. Diagnosis requires a comprehensive clinical evaluation, patient history, and diagnostic tests like nerve conduction studies or imaging to identify underlying issues. [120]

Trigeminal neuralgia is a specific form of neuropathic pain that influences the trigeminal nerve (cranial nerve V), responsible for facial sensation. This condition is characterized by sudden, severe, and stabbing pain episodes in the face, often triggered by mild stimuli such as touching the face, chewing, or speaking. The pathophysiology typically involves compression of the trigeminal nerve by blood vessels, leading to demyelination and erratic nerve signaling. Diagnosis is primarily clinical, supported by imaging studies like MRI to rule out compressive lesions or secondary causes. [121]

Understanding the distinctions between trigeminal neuralgia and general neuropathic pain is crucial for proper diagnosis and treatment. While trigeminal neuralgia requires specific targeted therapies due to its unique presentation and pathophysiology, neuropathic pain management often involves addressing the underlying condition causing the nerve damage or dysfunction. Effective treatment strategies for both types of pain require a comprehensive approach tailored to the individual patient's needs.

Squamous Cell Carcinoma of the Head and Neck

Squamous cell carcinoma (SCC) of the head and neck is a prevalent malignancy that affects areas including the larynx, pharynx, paranasal sinuses, oral cavity, and skin. It ranks as the sixth most common cancer globally. [118]

Over the past few decades, there has been an evident escalation of oropharyngeal cancer cases, particularly in younger individuals under 45, a trend often linked to human papillomavirus (HPV) infection. HPV-positive oropharyngeal tumors generally exhibit better treatment responses and survival rates compared to their HPV-negative counterparts.

The primary threats for SCC include alocohol usage, cigarettes and HPV infection. Other risk factors include exposure to certain chemicals, insufficient oral hygiene, and a family history of cancer. Patients often present with symptoms such as persistent sore throat, difficulty swallowing, unexplained weight loss, ear pain, and the presence of a lump in the neck. Any patient exhibiting these symptoms should be referred to an otorhinolaryngologist for further evaluation. [122]

Diagnosis typically includes a combination of physical examinations, imaging studies (like MRI and CT scans), and biopsy procedures to confirm the presence of malignancy. Identifying the HPV status of the tumor is also crucial for prognosis and treatment planning.

The treatment of squamous cell carcinoma (SCC) has been enhanced by the use of biological agents. Monoclonal antibodies like cetuximab target the epidermal growth factor receptor (EGFR), blocking tumor growth and proliferation when combined with radiation or chemotherapy. Immune checkpoint inhibitors such as pembrolizumab and nivolumab block the PD-1 pathway, boosting the immune system's ability to recognize and destroy cancer cells, particularly in recurrent or metastatic SCC. These targeted therapies offer better efficacy and lesser side effects compared to traditional chemotherapy. [123, 124]

The management of SCC requires a multidisciplinary approach to optimize outcomes. Early detection and accurate diagnosis are critical in formulating an effective treatment plan. Gene therapy holds significant promise for improving survival rates and quality of life for patients with SCC. Ongoing research and clinical trials are essential to refine these therapies and expand their applicability, ultimately offering hope for more effective management and potential cures for SCC of the head and neck.

Orthodontic tooth movement

Orthodontic tooth movement (OTM) relies on the dynamic reshaping of the periodontal ligament (PDL) and alveolar bone, processes orchestrated by osteoclasts and osteoblasts. Osteoclasts, originating from hematopoietic cells, specialize in bone resorption, crucial for accommodating tooth movement. In contrast, osteoblasts, derived from stromal cells, are responsible for bone formation, essential for stabilizing teeth in their new positions.

Central to this bone remodeling process is the intercommunication between receptor activator of nuclear factor kappa-B (RANK) and its ligand (RANKL). Osteoblasts express RANKL on their surface, which binds to RANK receptors on osteoclast precursors. This binding stimulates the differentiation of these precursors into mature, multinucleated osteoclasts, initiating bone resorption at the pressure side of the tooth movement. [125]

Counteracting the RANK-RANKL interaction is osteoprotegerin (OPG), a soluble receptor produced by osteoblasts. OPG performs as a decoy receptor for RANKL, inhibiting its binding to RANK and thereby preventing osteoclast formation and bone resorption. This delicate balance between RANKL, RANK, and OPG regulates the pace and extent of bone remodeling during orthodontic treatment. [126]

Biological agents utilized in orthodontics often target these regulatory pathways to influence tooth movement. For example, prostaglandins can modulate RANKL expression or directly affect osteoclast differentiation, potentially accelerating bone remodeling and facilitating faster tooth movement. Other agents under investigation include parathyroid hormone analogs and cytokines, which may enhance bone turnover and promote more efficient orthodontic outcomes. [127]

Understanding these intricate biological processes is critical for optimizing orthodontic treatment strategies. By targeting specific molecular pathways involved in bone remodeling, clinicians can potentially shorten treatment durations, minimize adverse effects such as root resorption, and improve overall treatment outcomes. Future research aimed at refining the use of biological agents in orthodontics holds promise for advancing patient care and achieving more predictable and efficient orthodontic tooth movement.

2.4.3. Side effect of biological agents

As we have seen, biological agents, including monoclonal antibodies, growth factors, cytokines, and others, exert their therapeutic effects by targeting specific cellular pathways involved in tissue regeneration, immune modulation, and disease progression. While they offer promising therapeutic benefits, their use is associated with potential side effects that require careful consideration, especially in the context of oral health.

One of the primary concerns with biological agents is their potential to induce immune responses in patients. Monoclonal antibodies, for instance, can trigger hypersensitivity reactions ranging from mild rashes to severe anaphylaxis. In dental applications, allergic reactions can manifest as oral mucosal swelling, erythema, or even oral ulcerations, affecting patient comfort and treatment outcomes.

Biological agents may compromise immune surveillance, increasing susceptibility to infections. Patients receiving immunosuppressive biological therapies are at heightened risk of developing oral infections such as candidiasis (oral thrush) and herpes simplex virus reactivation. Proper oral hygiene and vigilant monitoring are essential to mitigate infection risks in these individuals.

Local side effects within the oral cavity can include mucositis, gingivitis, and altered taste perception. Mucositis, often associated with chemotherapy and immune checkpoint inhibitors, manifests as painful oral ulcers and mucosal inflammation, compromising oral function and quality of life. Gingivitis and periodontal inflammation may also occur due to systemic medications affecting immune responses or local microbiota. [128]

In conclusion, while biological agents offer significant therapeutic advancements in dentistry and medicine, their use necessitates careful consideration of potential side effects. Clinicians must weigh the benefits against risks, tailor treatment regimens based on individual patient factors, and maintain vigilant monitoring to optimize patient safety and oral health outcomes. Continuing research and clinical vigilance are essential to refine therapeutic strategies and mitigate adverse effects associated with these innovative therapies.

3. CONCLUSION

Immunosuppressive therapy has undergone significant evolution since its inception, continuously expanding its scope to address a variety of systemic diseases. Within the realm of dental medicine, there exist numerous oral conditions that necessitate the application of immunosuppressive treatments for effective management. It is imperative for dental practitioners to possess a comprehensive understanding of the mechanisms of action of these drugs to ensure the safe and efficacious treatment of their patients.

Corticosteroids are the most frequently employed immunosuppressive drugs in dental medicine. These agents are widely utilized in the management of dermatoses with oral manifestations, extensive ulcerations, the reduction of orofacial pain, and post-surgical conditions. Their anti-inflammatory properties make them indispensable in these contexts.

However, when a more potent anti-inflammatory effect is required, calcineurin inhibitors are introduced. These inhibitors are notably effective in the rapid suppression of the erosive form of oral lichen planus, providing quick relief and control of symptoms.

In recent years, the introduction and expanding application of biological agents have significantly broadened the clinical indications for immunosuppressive therapy in specialized branches of medicine, including dental medicine. These biological agents have shown particular promise in the treatment of oral manifestations of autoimmune diseases such as pemphigus vulgaris and systemic lupus erythematosus. Their efficacy is especially pronounced in cases where traditional immunosuppressive drugs yield suboptimal results.

The successful management of these complex cases necessitates a multidisciplinary approach, involving close collaboration between dental professionals and specialists from other medical disciplines. Such collaboration ensures a holistic treatment approach that addresses all aspects of the patient's health. Additionally, comprehensive patient education plays a critical role in the management of these therapies. Educating patients about the importance of adherence to treatment protocols, potential side effects, and the need for regular monitoring can significantly enhance treatment outcomes.

Properly administered immunosuppressive therapy requires meticulous monitoring and individualized dose adjustments to each patient. This careful approach aims to minimize adverse effects while maximizing therapeutic efficacy. Regular follow-ups and adjustments based on the patient’s response to treatment are crucial components of this process.

In conclusion, the integration of immunosuppressive therapies into dental medicine represents a significant advancement that demands a multidisciplinary approach and continuous education for healthcare providers. As the field of immunosuppressive therapy continues to advance, dental professionals must remain informed and adept at managing these powerful therapeutic agents. This ongoing commitment to professional development and interdisciplinary collaboration is essential to ensuring the highest standards of patient care, optimizing outcomes, and minimizing risks associated with immunosuppressive treatments. The future of dental medicine will undoubtedly continue to benefit from these advancements, leading to improved management of complex oral conditions and overall patient health.

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