



## Immunosuppressant Drugs: Role in Periodontium

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**ABSTRACT :** The periodontium and periodontal disease activity can be affected by systemic drug therapy. Immunosuppressant drugs are one among such category. These drugs in common, influences the response of gingival and periodontal tissues to bacterial plaque. An extremely effective and most commonly used immunosuppressant drug for organ transplant procedures is cyclosporine A. The drug is also associated with various untoward effects, including gingival overgrowth. Corticosteroids are another major drug category, which may either exert its action as an immunosuppressant or as an anti-inflammatory agent. This review considers the pharmacokinetics, pharmacodynamics, and unwanted effects of immunosuppressants, on the gingival tissues.

**Key words:** Periodontium, Periodontal disease, Immunosuppressants, Cyclosporin A( CsA ), Corticosteroids, Gingival overgrowth.

### Introduction

Periodontal disease is the result of an interaction between bacterial plaque and its products and the resultant inflammatory and immunological changes within the periodontal tissues.<sup>1,2</sup> The nature and the pathogenesis of periodontal disease can be affected by a variety of drugs, especially those that interact with immune and inflammatory responses. Hence, such drug therapy can modify the effect of bacterial plaque on the periodontal tissues. In addition, some drugs can have adverse effects on the periodontal tissues such as gingival overgrowth.

The purpose of this review is to investigate the effect of systemic therapy of immunosuppressants on periodontal tissues, and where possible to relate such changes to the pharmacodynamics of the drugs involved. Reports from the literature have shown that immunosuppressants act on various components of the immune system causing selective inhibition and suppression. Drugs used for this purpose include corticosteroids (mainly prednisone and prednisolone), azathioprine and more recently cyclosporin.

### Immunosuppressants

Immunosuppressant drugs, as their name suggests, are a group of compounds that target the immune system and suppress various aspects of this system. They have three main indications in medicine:

- to suppress rejection in organ-transplant patients.
- in the treatment of a variety of chronic inflammatory conditions, where suppression of the immune response may help to alleviate symptoms.
- in the management of autoimmune diseases.

There are several drugs that can affect the immune system and which have therapeutic applications.

List of immunosuppressants used in medical practice and their indications.<sup>3</sup> Table 1

### Immunosuppressants and the Periodontium

Early studies, in the 1970s and 1980s, showed that patients on long-term immunosuppressants (usually azathioprine and prednisolone) were afforded some degree of protection against periodontal breakdown. The more selective immunosuppressants (cyclosporine and tacrolimus) may not afford the same degree of protection against periodontal breakdown.

However, with cyclosporine, the unwanted effect of gingival overgrowth will inhibit plaque removal and thus create a somewhat different environment for periodontal disease. Animal studies have suggested that cyclosporine can have an adverse effect on alveolar bone homeostasis, resulting in increased osteoclasia and a decrease in bone formation.<sup>4</sup>

As with other categories of systemic medication, there is little or no therapeutic indication for the use of immunosuppressants in the management of periodontal disease. As with other anti-inflammatory agents, the main interest in these drugs is what their pharmacodynamics can tell us about the pathogenesis of periodontal disease and periodontal breakdown. Their unwanted effects would exclude any indication for their use in the management of periodontal disease.

### **Antiproliferative Immunosuppressants**

The two main examples of this category of immunosuppressants are azathioprine and mycophenolatemofetil.

#### **Azathioprine**

Azathioprine is a purine derivative which can be considered as a prodrug. The drug is first metabolized to 6-mercaptopurine and further metabolized by the enzyme thiopurinomethyltransferase to the pharmacologically active 6-thioguanine nucleotide. The latter suppresses the immune system by inhibiting DNA synthesis in lymphocytes.

#### **Unwanted Effects**

Increased susceptibility to infections, especially opportunistic infections, and bone marrow suppression. A drug-induced depression of platelets could lead to petechial hemorrhages and also to profuse bleeding from the gingival tissues, especially upon any form of gingival manipulation. A reduction in the white cell count will increase the risk of oral ulceration and periodontal breakdown. Azathioprine-induced myelosuppression is most likely to manifest in the early stages of treatment and is managed by reducing the dose.

#### **Mycophenolate Mofetil**

Mycophenolatemofetil is considered a prodrug and is hydrolyzed to mycophenolic acid. Mycophenolic acid reduces both B- and T-cell proliferation by inhibiting the production of guanine nucleotide. It has been suggested that mycophenolatemofetil may be effective against both acute and chronic organ rejection.<sup>5</sup>

#### **Unwanted Effects**

The most significant unwanted effect are myelosuppression and thrombocytopenia.

Patients on this drug will undergo regular haematological screening and if any form of periodontal surgery is planned then a blood test should be requested before the procedure, with specific attention given to the platelet count. Also associated with a high prevalence of gastrointestinal problems, especially vomiting. This can readily lead to dental erosion, and preventive measures need to be put into place to avoid the outcome of this unwanted effect.

### **Calcineurin Inhibitors**

Calcineurin is a protein phosphatase that activates T-cells of the immune system. It is the target of drugs such as cyclosporine and tacrolimus.

#### **Cyclosporine**

Cyclosporine has had a dramatic effect on patients undergoing organ-transplant surgery, on subsequent graft survival and on quality of life. The main mode of action of cyclosporine is its selective inhibitory effect on transcription of the interleukin-2 gene.

- There is decreased clonal proliferation of T-cells.
- Reduced induction of, and clonal proliferation of, cytotoxic cells from CD8+ precursor T-cells.
- Reduced function of the effector T cells and some reduction in T-cell-dependent B-cell responses.

#### **Unwanted Effect**

From the periodontal perspective, the main interest in cyclosporine is the unwanted effect of gingival overgrowth. This was first reported in the early 1980s and has been the subject of extensive research. Other unwanted effects of cyclosporine include nephrotoxicity, hypertension and an increased risk of skin malignancies. CsA elicited enlargement and overgrowth of gingiva in human organ transplant recipients.<sup>6</sup> Recent investigations reported incidence to be approximately 25% to 30%.<sup>7</sup>

#### **Tacrolimus**

Tacrolimus is a macrolide antibiotic that also inhibits calcineurin. It is more potent than cyclosporine, and is now replacing cyclosporine as the treatment of choice to prevent graft rejection in organ transplantation.

Immunosuppressant	Indications
Azathioprine	Transplant patients, inflammatory bowel disease, rheumatoid arthritis, severe refractory eczema
Mycophenolatemofetil	Prophylaxis of acute renal, hepatic and cardiac transplant rejection
Prednisolone	Prevention of graft rejection
Cyclosporine	Prevention of graft rejection, treatment of graft-vs.-host disease, severe ulcerative colitis, rheumatoid arthritis, severe skin disorders
Sirolimus	Prophylaxis of organ rejection in kidney allograft recipients
Tacrolimus	Prophylaxis of organ graft rejection in liver, kidney and heart allograft recipients and for allograft rejection resistant to conventional immunosuppressant regimens, moderate to severe eczema

**Table : 1 List of immunosuppressants used in medical practice and their indications**

Unwanted effects of tacrolimus include gastrointestinal disturbances, hypertension, nephrotoxicity and metabolic disturbances.

**Corticosteroids**

Corticosteroids are a group of drugs that are structurally and pharmacologically related to the

endogenous hormone cortisol. There are several corticosteroids, each with different potencies and applications.

Corticosteroids are extensively used in many aspects of medicine. They can be applied topically, by inhalation, orally and parenterally.

**Pharmacological properties**

Therapeutic usage correlates with their anti-inflammatory and immunosuppressive actions. Anti-inflammatory action is mediated via

- The ability to stimulate the production of a protein known as lipocortin-1 (annexin A1) <sup>8</sup>. Lipocortin suppresses the enzyme phospholipase A2. Thus stimulation of lipocortin, blocks the production of various eicosanoids ( prostaglandins and leukotrienes).
- Also suppress the enzymes cyclooxygenase-1 and cyclooxygenase-2, further reducing eicosanoid synthesis.

A list of those widely prescribed in medical practice is given in Table 2.

**Immunosuppressant action is mediated by:**

- Suppress the cell-mediated response by inhibiting the genes that code for cytokines interleukin-1 to -6, interleukin-8 and interferon-γ resulting in reduced T-cell proliferation.

Corticosteroid	Indication
Hydrocortisone	Adrenocortical insufficiency, shock, hypersensitivity reaction, asthma, inflammatory bowel disease, skin disorders, rheumatic diseases
Cortisone acetate	Steroid replacement therapy
Betamethasone	Suppression of inflammatory and allergic disorders, congenital adrenal hyperplasia, oral ulceration
Deflazacort	Suppression of inflammatory and allergic disorders
Dexamethasone	Suppression of inflammatory and allergic disorders, cerebral edema, nausea and vomiting from chemotherapy, rheumatic diseases
Prednisolone	Suppression of inflammatory and allergic disorders, asthma, immunosuppression, rheumatic diseases
Methylprednisone	Suppression of inflammatory and allergic disorders, inflammatory bowel disease, rheumatic diseases
Triamcinalone	Suppression of inflammatory and allergic disorders, skin conditions

**Table 2 : A list of those widely prescribed in medical practice is given**

- Humoral immunity is also suppressed, resulting in a reduction in B-cell-clone expansion and antibody synthesis and reduced activation of T-lymphocytes.<sup>9</sup>

Combined immunosuppressant and anti-inflammatory actions are mediated by activation of the glucocorticoid receptor. Activated glucocorticoid receptors up-regulate the expression of anti-inflammatory proteins and suppress the expression of pro-inflammatory proteins.<sup>10</sup>

**Corticosteroids And The Periodontium**

Early animal studies showed that systemic cortisone injections have a significant effect on periodontal tissues<sup>11</sup>, including induction of alveolar bone loss and reduction in the numbers of osteoblasts and fibroblasts and of the intercellular matrix. This condition is identical to the bone

status seen in osteoporosis and has been confirmed in further animal studies, which demonstrated that anti-osteoporotic drugs (calcitonin and alendronate) prevented corticosteroid-induced osteoporosis.<sup>12</sup> Other animal studies also showed that systemic cortisone could attenuate the plaque-induced inflammatory responses in the periodontal tissues.

Human studies on patients on long-term steroid therapy for medical conditions demonstrate some anti-inflammatory effects of corticosteroids on gingival tissues, not necessarily a reduction in the rate of periodontal breakdown.<sup>11</sup>

Animal studies have provided some insight into the relationship among stress, cortisol production and periodontal breakdown.<sup>13</sup> Rats that showed a low response to stress developed significantly less periodontal breakdown than those that showed a high

Target	Effect
Carbohydrate metabolism	Decreased uptake of glucose and increased gluconeogenesis, leading to an increased risk of diabetes
Protein	Decreased protein synthesis and increased protein breakdown, especially in muscles, causing muscle wasting
Bone	Osteoporosis
Gastric mucosa	Increased risk of peptic ulceration
Adrenal cortex	Suppression leading to an increased risk of an adrenocortical crisis
Fat	Redistribution of body fat causing so-called moon faces and Buffalo hump
Skin	Thinning of skin and an increased risk of acne
Wound healing	Impaired
Immune system	Immunosuppression, increased risk of opportunistic infections
Cardiovascular system	Hypertension
Neurological	Mood changes and insomnia
Blood vessels	Easy bruising

**Table 3. List of unwanted effects of steroids**

response.

The same group subsequently demonstrated a glucocorticoid receptor antagonist reduced periodontal breakdown in ligature-induced periodontitis in rats.<sup>14</sup> The authors concluded that hypothalamic–pituitary–adrenal axis hyper-activation is one mechanism by which periodontal disease susceptibility may be increased.

Stress and salivary cortisol have been measured in an adult population suffering from periodontitis.<sup>15</sup> Salivary cortisol levels were positively associated with an increase in psychological stress and in the

extent and severity of periodontitis.

Corticosteroids are very potent and valuable group of drugs that are used to treat a variety of medical conditions. Their interest, in periodontal terms, is on their anti-inflammatory actions and whether such actions can provide an insight into the pathogenesis of plaque-induced gingival inflammation and periodontal disease expression. Therefore, such drugs have been used as a pharmacological tool and do not have a place in the management of periodontal disease.

**Unwanted Effects Of Corticosteroids**

Steroids have a range of unwanted effects, which are listed

in Table 3. Of particular concern to the periodontist are the unwanted effects of steroid-induced osteoporosis and the risk of adrenocortical suppression. Table 3.

### **Corticosteroid-Induced Osteoporosis**

Corticosteroids have a significant effect upon bone metabolism. They increase bone resorption, inhibit bone formation, decrease the intestinal absorption of calcium ions and modify vitamin D metabolism. The net result is an increased risk of osteoporosis, which is considered a risk factor for periodontal disease, especially an increased risk of tooth loss.<sup>16</sup> It has been estimated that 20–30% of patients on long-term steroid therapy will develop osteoporosis.<sup>17</sup> The risk is higher in patients >60 years of age and also in women.

Corticosteroid-induced osteoporosis can be managed by dietary supplements of calcium and

vitamin D and also by bisphosphonates. Issues relating to the use of bisphosphonates and their unwanted effects are discussed later.

### **Conclusion**

This review has primarily focused on those immunosuppressant drugs that affect the inflammatory cascade and on the impact, if any of such medication on plaque-induced inflammation of the periodontal tissues and disease progression. Immunosuppressants do affect the response of gingival and periodontal tissues to bacterial plaque. They do not abolish the reaction of the tissues to plaque, but appear to dampen down inflammatory reactions. The specific pharmacodynamics of immunosuppressants may provide further insight into the pathogenesis of periodontal inflammation and breakdown.

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