



Immunosuppressants

NITA CHAINANI-WU, DMD, MS, PHD, AND TIMOTHY C. WU, DMD, MS

ABSTRACT This paper provides a brief introduction to some of the common immunosuppressants used in oral medicine, the prevention and treatment of oral adverse effects of immunosuppressants, and considerations for dental treatment in patients taking immunosuppressants.

AUTHORS

Nita Chainani-Wu, DMD, MS, PHD, is a health sciences assistant clinical professor, Orofacial Sciences Department, University of California, San Francisco; a research associate and project director at the Preventive Medicine Research Institute, Sausalito Calif; and in private practice, oral medicine in Sunnyvale, Calif.

Timothy C. Wu, DMD, MS, is in private practice, periodontics, in Sunnyvale, Calif.

We live in a world where it appears that “we” and “the environment” are clearly separated. On closer inspection, that separation is not all that clear. Are the microorganisms we call “normal flora” that populate our bodies part of us or the environment? We carry on and within our bodies more bacteria than cells. And this is when we apparently are in perfect health. When does the food ingested go from being a part of the environment to a part of our “self”?

The immune system has the seemingly impossible task of distinguishing our “self” from “nonself.” The most obvious “nonself” entities include pathogenic microorganisms that are not part of the normal flora. The immune surveillance also helps keep the amount and proportion of normal flora in check. Most of the time it does these things very well. And of course, we want our immune system to keep doing that very well. A good immune system is the foundation of good health.

However, sometimes our immune system seems to stop recognizing some part/parts of our body as “self” and starts attacking these tissues. This can result in a spectrum of conditions broadly called autoimmune diseases. When this happens, a suppression of the immune system can help control these autoimmune diseases. Some of the well-known autoimmune diseases include rheumatoid arthritis, lupus erythematosus, multiple sclerosis, and Hashimoto’s disease.

Also, in some individuals the immune system can react strongly against substances that don’t have much potential to otherwise be harmful such as dust mites, peanuts, pollen, and many others. This strong immune reaction can be very harmful — even life threatening — and this can be in response to benign substances that most other people can tolerate without any harmful effects.

The management of such allergic reactions (including allergy-induced asthmatic reactions) may include the use of immunosuppressive medica-

TABLE 1

Systemic Immunosuppressant Medications Used in the Treatment of Oral Diseases

Name of Medication	Indications in Oral Diseases	Common Adverse Effects
Glucocorticosteroids ¹ e.g., prednisone	Pemphigus vulgaris, mucous membrane pemphigoid, oral lichen planus, erythema multiforme, lichenoid drug reactions, major aphthous ulcerations, Behçets syndrome.	Short-term use (<3 weeks): insomnia, mood changes, fluid retention, weight gain, hyperglycemia. Long-term use: osteoporosis, hypertension, hyperglycemia, gastrointestinal disturbances, delayed healing, increased risk of infections, aseptic necrosis, cataracts, psychiatric problems, suppression of the hypothalamus-pituitary-adrenal axis.
Azathioprine ²	Used as a steroid-sparing agent in combination with systemic glucocorticosteroids for long-term use in chronic conditions like pemphigus vulgaris, mucous membrane pemphigoid, lichen planus, or recurrent major aphthous ulcerations.	Bone marrow suppression especially in individuals with low expression of TPMT (thiopurine methyl transferase); hepatotoxicity, gastrointestinal disturbances, increased risk of hematological malignancies and infections.
Mycophenolate mofetil ³	Used as a steroid-sparing agent in combination with systemic glucocorticosteroids for long-term use in chronic conditions like pemphigus vulgaris, mucous membrane pemphigoid, lichen planus, or recurrent major aphthous ulcerations.	Gastrointestinal disturbances, bone marrow suppression, genito-urinary effects, increased risk of infections.
Cyclophosphamide ⁴	Wegener's granulomatosis, usually in combination with prednisone for induction of remission.	Bone marrow suppression, increased risk of infections and malignancies, mucositis, renal toxicity, gastrointestinal disturbances, hepatotoxicity, urinary system effects and respiratory system effects.
Methotrexate ^{4,5}	Wegener's granulomatosis, usually in combination with prednisone for maintenance of remission. In less severe cases it may be used for induction of remission instead of cyclophosphamide.	Hepatotoxicity, mucositis, bone marrow suppression, increased risk of infections and malignancies.

tions, along with avoidance of the allergens, depending on the severity and the chronicity of the conditions.

The other situation when suppression of the immune system is desirable is when a person receives an organ or hematopoietic cell transplant. The immune system's normal function of attacking nonself results in an attack on the transplanted tissue and a subsequent rejection.

Therefore, in case of autoimmune diseases and organ and hematopoietic cell transplantation, immune suppression is desirable. Transplant patients are routinely on immunosuppressant medications, and individuals with allergies and

autoimmune diseases may be on immunosuppressants depending on the chronicity and severity of their conditions.

This paper provides a brief introduction to some of the common immunosuppressants used in oral medicine, the prevention and treatment of oral adverse effects of immunosuppressants and considerations for dental treatment in patients on immunosuppressants.

Common Immunosuppressants Used in Oral Medicine

A number of autoimmune inflammatory conditions affect the oral mucosa, and depending on the severity and chronicity

of these conditions, the use of immunosuppressant medications may be indicated.

Due to the possibility of adverse effects with use of these medications, especially in those with underlying medical conditions, the benefits versus the risks should be carefully considered before use and only those clinicians with training and experience in use of these medications should prescribe them. When dealing with systemic conditions that affect the oral cavity (e.g., pemphigus vulgaris, Wegener's granulomatosis) and with patients with serious or complex medical conditions, it is appropriate to involve the patient's physician(s) in a team approach for management of the patient.

TABLE 2

Use of Immunosuppressants for Treatment of Some of the More Common Oral Mucosal Conditions

Diseases Affecting the Oral Mucosa	Treatment Options Using Immunosuppressive Medications
Aphthous ulcers	<p>Patients with frequent, multiple or major aphthous ulcerations may benefit from treatment with glucocorticosteroids.</p> <p>Topical preparations such as fluocinonide 0.05% or clobetasol 0.05% ointment mixed in equal parts with orabase B, applied to the affected areas at the first symptom of an impending ulceration may cut down healing time significantly, and may be all that is required for most patients with this condition.</p> <p>Intralesional steroids such as betamethasone for large painful ulcerations can be helpful to hasten healing. For severe flares with multiple ulcerations, systemic corticosteroids can be used, prednisone 40 mg to 60 mg daily for up to a week is usually sufficient. However, for very frequent recurrences of severe flares a more customized treatment plan may be required with consideration of longer term treatment with prednisone along with a steroid-sparing immunosuppressive agent.</p>
Oral lichen planus, mucous membrane pemphigoid	<p>These diseases maybe well-maintained with topical glucocorticosteroids, such as fluocinonide 0.05% or clobetasol 0.05% ointment mixed in equal parts with orabase B, and/or a mouthrinse such as elixir of dexamethasone 0.5 mg/5 ml.</p> <p>For initial control of symptoms and for occasional flare-ups a short course of prednisone 40 mg to 60 mg daily for about 1 week can be helpful (FIGURES 1A-B). In more severe disease, a longer course of prednisone in combination with a steroid-sparing immunosuppressive agent such as azathioprine or mycophenolate mofetil may be necessary.</p>
Oral erythema multiforme	<p>In many cases oral erythema multiforme responds dramatically to systemic glucocorticosteroids and a short course of prednisone 40 mg to 60 mg daily for about 1 week can result in significant improvement or complete resolution. For very frequent recurrences or a chronic presentation a longer course of immunosuppressants can be considered or in cases of herpes-associated erythema multiforme prophylactic anti-virals can be used.</p>
Hypersensitivity reactions	<p>These are treated by discontinuation of the agent triggering the hypersensitivity reaction. Topical or systemic glucocorticosteroids can be used to hasten resolution of symptoms if necessary.</p>
Pemphigus vulgaris	<p>Long-term immunosuppression is generally required for treatment of pemphigus vulgaris. Relatively high starting doses of prednisone (60 mg to 80 mg daily) may be needed, along with a steroid-sparing immunosuppressive agent such as azathioprine (50 mg to 100 mg daily) or mycophenolate mofetil (2 g to 3 g daily). In case of very severe disease higher initial doses may be needed. Taper of the medications is done slowly and is based on clinical response. Close monitoring is needed especially until the disease process and medications are stabilized. The topical steroid pastes and mouthrinse mentioned above can also be used for control of oral lesions in addition to the systemic medications if necessary.</p>
Wegener's granulomatosis	<p>For induction of remission, cyclophosphamide in combination with glucocorticosteroids is used. In less severe cases methotrexate can be used instead of cyclophosphamide. For maintenance therapy methotrexate or azathioprine alone or usually in combination with glucocorticosteroids are used. In the case of isolated upper respiratory tract involvement cotrimoxazole is a treatment option. Doses vary significantly based upon disease severity.⁴</p>

The systemic immunosuppressant medications commonly used in oral medicine, common indications, and common adverse effects are summarized in **TABLES 1 AND 2**. Periodic tests including, complete blood counts and liver function tests are necessary to monitor for these adverse effects.²⁻⁴ For long-term glucocorticosteroid use, baseline tuberculin testing as well as baseline and

periodic tests of bone mineral density (DEXA scans), blood pressure monitoring, blood glucose monitoring and periodic eye exams are recommended.¹

Topical preparations of immunosuppressant medications including glucocorticosteroids, cyclosporine and tacrolimus are also used for treatment of oral inflammatory conditions in order to avoid the side effects associated with systemic use.

Oral Adverse Effects of Immunosuppressants Medications

Some oral adverse effects are commonly seen with certain immunosuppressants.

Cyclosporin-induced gingival hyperplasia is a well-known adverse effect of this medication, which is commonly used post-transplantation.⁶⁻⁸ It can be prevented with good oral hygiene and plaque control.^{9,10} Treatment includes scaling and surgical



FIGURE 1A. Oral lichen planus before treatment with prednisone (60 mg per day for one week).



FIGURE 1B. Oral lichen planus after treatment with prednisone (60 mg per day for one week).



FIGURE 2A. Cyclosporin-induced gingival hyperplasia before surgical periodontal treatment.



FIGURE 2B. Cyclosporin-induced gingival hyperplasia after surgical periodontal treatment.

excision if necessary¹¹⁻¹³ (FIGURES 2A-B).

Use of topical and inhalation glucocorticosteroids can predispose to development of oral candidiasis.¹⁴ This can be prevented by applying topical steroids only on the affected areas on the oral mucosa in the smallest amount necessary, and after use of inhalation steroids rinsing out the mouth with water or a mouthrinse. Oral candidiasis is treated with topical anti-fungals (e.g., nystatin, clotrimazole) or systemic anti-fungals (e.g., fluconazole, ketoconazole).

Methotrexate used both for treatment of malignancies and in lower doses for rheumatoid arthritis, psoriasis and other conditions commonly causes oral ulcerations.¹⁵ This can be prevented and/or treated by use of supplemental folic acid or folinic acid. However, in severe cases of methotrexate-induced oral ulcerations, decreasing the dose or discontinuation of the medication may be necessary.

Cyclophosphamide is used in cancer chemotherapy and also in some autoimmune or inflammatory conditions. Oral ulcers and loss of taste are common side effects of this medication, which generally resolve after completion of treatment.⁴

Considerations for Dental Treatment of Patients on Immunosuppressive Medications

The underlying reasons for immunosuppressive treatment are very diverse, and patients taking these medications range from being in relatively good health to being seriously ill.

Cancer chemotherapeutic agents also have the side effect of immunosuppression and patients undergoing chemotherapy for malignancies are immunosuppressed to varying degrees depending on the treatment protocol.

The medical history of patients on immunosuppressive medications, including the underlying medical problems, as well as dose and duration of immunosuppressive therapy is very important in evaluating possible risks during dental treatment.

Depending on these factors, the patient's susceptibility to infections and bleeding, and the ability to tolerate stress and medications may vary. The need for pre- or perioperative medications such as antibiotics or glucocorticosteroid supplementation, and the need for laboratory evaluations also vary based on

these factors as well as on the extent of the planned dental surgical procedures.

For routine minor dental procedures, perioperative glucocorticosteroid supplementation is not recommended for patients with current or recent use of glucocorticosteroids. The usual daily dose of glucocorticosteroid should be taken prior to (within two hours before) the dental procedure, which, preferably, should be scheduled in the morning. However, for extensive dental procedures and for surgical procedures, perioperative glucocorticosteroid supplementation is recommended for patients with current or recent corticosteroid use. The details on glucocorticosteroid supplementation are beyond the scope of this paper, however relevant published recommendations are included in the bibliography.¹⁶⁻²¹

A consultation with the patient's physician(s) may be necessary to get a clear understanding of the patient's medical history and current treatment, as well as suggestions on how to medically compensate for dental procedures that may have an adverse medical impact, particularly in those patients who require extensive dental surgical procedures. Such consultations can also be helpful in making decisions on the appropriate perioperative, short-term or long-term medications for patients with complex medical histories and/or multiple medication use.

Adjustment of the usual dosage of commonly prescribed medications in dentistry may be needed in some patients, particularly those with a relative contraindication to the drug, and/or compromised renal or hepatic function. The patient's physician(s) can calculate the adjusted dose for the patient based on current renal and/or hepatic function or other relevant parameters. Periodic laboratory tests may also be necessary during the time of administration of the

drug, and the dentist and physician can work together to monitor the therapeutic effects of the drug and any adverse effects requiring modification of the dosage.

In case of interaction of necessary medications with the patient's current medication(s), in some situations the patient's physician may be able to incorporate the needed medications; this may involve a temporary or a longer-term change in the patient's other medications, if appropriate. ■■■■

REFERENCES

1. Jackson S, Gilchrist H, et al, Update on the dermatologic use of systemic glucocorticosteroids. *Dermatologic Therapy* 20(4):187-205, 2007.
2. Wise M, Calle JP, Azathioprine: A guide for the management of dermatology patients *Dermatologic Therapy* 20(4):206-15, 2007.
3. Zwerner J, Fiorentino D, Mycophenolate mofetil. *Dermatologic Therapy* 20(4):229-38, 2007.
4. White ES, Lynch JP, Pharmacologic therapy for Wegener's granulomatosis. *Drugs* 66(9):1209-28, 2006.
5. Bangert CA, Costner MI, Methotrexate in dermatology. *Dermatologic Therapy* 20(4):216-28, 2007.
6. Rateitschak-Plüss EM, Hefti A, et al, Initial observation that cyclosporin-A induces gingival enlargement in man. *J Clin Periodontol* 10:237-46, 1983.
7. Tyldesley WR, Rotter E, Gingival hyperplasia induced by cyclosporin-A. *Br Dent J* 157:305-9, 1984.
8. Seymour RA, Jacobs DJ, Cyclosporin and the gingival tissues. *J Clin Periodontol* 19:1-11, 1992.
9. McGaw T, Lam S, Coates J, Cyclosporin-induced gingival overgrowth: Correlation with dental plaque scores, gingivitis scores, and cyclosporin levels in serum and saliva. *Oral Surg Oral Med Oral Pathol* 64:293-297, 1987.
10. Seymour RA, Smith DG, The effect of a plaque control program on the incidence and severity of cyclosporin-induced gingival changes. *J Clin Periodontol* 18:107-10, 1991.
11. Kantarci A, Cebeci I, et al, Clinical effects of periodontal therapy on the severity of cyclosporin A-induced gingival hyperplasia. *J Periodontol* 70:587-93, 1999.
12. Pernu HE, Pernu LM, Knuutila ML, Effect of periodontal treatment on gingival overgrowth among cyclosporine A-treated renal transplant recipients. *J Periodontol* 64:1098-100, 1993.
13. Mavrogiannis M, Ellis JS, et al, The efficacy of three different surgical techniques in the management of drug-induced gingival overgrowth *J Clin Periodontol* 33:677-82, 2006.
14. Chainani-Wu N, Silverman S Jr, et al, Oral lichen planus: Patient profile, disease progression and treatment responses. *J Am Dental Assoc* 132:901-9, 2001.
15. Kalantzis A, Marshman Z, et al, Oral effects of low-dose methotrexate treatment. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 100:52-62, 2005.
16. Gibson N, Ferguson J, Steroid cover for dental patients on

long-term steroid medication: Proposed clinical guidelines based upon a critical review of the literature. *Br Dent J* 197(11):681-5, 2004.

17. Little J, Falace D, et al, Dental management of the medically compromised patient, sixth ed. Copyright 2002, Mosby, Inc.
18. Coursin D, Wood K, Corticosteroid supplementation for adrenal insufficiency. *JAMA* 287(2):236-40, 2002.
19. Miller C, Little J, Falace D, Supplemental corticosteroids for dental patients with adrenal insufficiency, reconsideration of the problem. *J Am Dent Assoc* 132:1570-9, 2001.
20. DeRossi S, Glick M, Lupus erythematosus: considerations for dentistry. *J Am Dent Assoc* 129:330-9, 1998.
21. Salem M, Tainsh R, et al, Perioperative glucocorticoid coverage, a reassessment 42 years after emergence of a problem. *Ann Surg* 219(4):416-25, 1994.

TO REQUEST A PRINTED COPY OF THIS ARTICLE, PLEASE CONTACT Nita Chainani-Wu, DMD, MS, PhD, 693 East Remington Drive, Suite B, Sunnyvale, Calif., 94087.