10.5005/jp-journals-10001-1117
REVIEW ARTICLE

Rationale in Usage of Immunomodulators for Management of Head, Face and Neck Cancers

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ABSTRACT

Recent advances in molecular biology have provided insight into the complex network of interaction that occurs within the immune system. The use of specific Immunomodulators to strengthen a deficient immune system or bolster a normal immune system presents a unique strategy for the treatment of various disorders that will clearly affect the practice of clinical medicine for many years to come. A major difficulty limiting the use of immunomodulators in clinical medicine has been the complexity of the immunoregulatory network in which modulation of one component usually perturbs the entire system, thus diminishing the specificity of the approach. Several immunomodulators are currently being tested in the treatment of the immune defect of the acquired immunodeficiency syndrome.

This article covers the types of immunomodulators, their mechanism of action and their applications.

Keywords: Immunosuppressants, Immunostimulants, Cell mediated immunity, Humoral immunity.

How to cite this article: Pagare SS, Singhi R, Vahanwala S Nayak CD. Rationale in Usage of Immunomodulators for Management of Head, Face and Neck Cancers. Int J Head and Neck Surg 2012;3(3):154-157.

Source of support: Nil

Conflict of interest: None declared

INTRODUCTION

'Synergy and serendipity often play a big part in medical and scientific advances.'

Julie Bishop

Immunomodulators weaken or modulate the activity of the immune system that, in turn, decreases the inflammatory response.

These drugs are appropriate for subjects who have:

- No respond to aminosalicylates, antibiotics or corticosteroids.
- Steroid-dependent disease or frequently required steroids.
- Experienced side effects with corticosteroid treatment.
- Perennial disease that does not respond to antibiotics.
- Fistulas (abnormal channels between two loops of intestine or between the intestine and another structure).
- A need to maintain remission.

An immunomodulator may be combined with a corticosteroid to speed up response during active flares of disease. Lower doses of the steroid are required in this case, producing fewer side effects. Corticosteroids also may be withdrawn more rapidly when combined with immunomodulators. For that reason, immunomodulators are sometimes referred to as '*steroid-sparing*' drug.[1,2]

Types of Immunomodulators

Immunosuppressants

Drugs which are used to suppress the immunity (Tables 1 and 2). Since, immunity confers resistance to disease, the

Table 1: Types of immunomodulators

Immunosuppressants		*Immunostimulants*	
Mechanism of action	*Drug category*	*Mechanism of action*	*Drug category*
Those which act by general suppression of all immune responses	Antimetabolites—azathioprine, methotrexate, cyclophosphamide, chlorambucil Nucleotide synthesis inhibitors—mycophenolate mofetil, leflunomide	Increasing the humoral antibody responses	Amantadine, tilorone BCG vaccine
		Enhancing the phagocytic activity of macrophages	Recombinant cytokines—interferons, interleukin-2
Those which are specific suppressants of certain immune responses	Antilymphocytic serum (ALS) cyclosporine, tacrolimus, sirolimus	Modifying the cell-mediated immune responses	Thalidomide, levamisole
Highly selective monoclonal antibodies	Depleting antibodies (against T cells, B cells or both)—muromonab, rituximab, antithymocyte globulin. Non-depleting antibodies and fusion proteins—daclizumab, basiliximab		
Those which reduce the unwanted reactions due to immune responses, by their anti-inflammatory actions.	Glucocorticoids—prednisolone thalidomide		

Table 2: Immunosuppressants

Drugs	*Mechanism of action*	*Side effects*	*Advantages/disadvantages*	*Other uses*
Cyclosporine	It selectively inhibits T lymphocyte proliferation, IL-2 and other cytokine production and response of inducer T cells to IL-1 without any effect on suppressor T cells	Gingival hyperplasia Hypertension Headache Precipitation of diabetes Hyperkalemia GI disturbances Tremors Hypertrichosis[3]	Disadvantages: Expensive	Multiple sclerosis Oral lichen planus[4] Paraneoplastic pemphigus Pemphigus vulgaris Aphthae ulcers[5] Psoriasis
Azathioprine	It disrupts the synthesis of DNA and RNA as well as the process of cell division; suppresses CMI	Myelosuppression and nausea (related to TPMT activity) Hepatotoxicity and hypersensitivity (unrelated to TPMT activity). Increased susceptibility to infections in patients with cyclosporine toxicity[6]	Advantages: Oral administration inexpensive Disadvantages: Slow onset side effect profile	Systemic lupus erythematosus Aphthous ulcer Pemphigus vulgaris Oral lichen planus
Methotrexate	It has a cell-specific action kills cell in S phase; primarily inhibits DNA synthesis, but also affects RNA and protein synthesis	Myelosuppression Hepatotoxicity Pneumonitis Alopecia Oral ulceration GI disturbances	Advantages: Oral administration Inexpensive Disadvantages: Slow onset	Pemphigus vulgaris Systemic lupus erythematosus Uveitis Psoriasis Cancer of tongue Pemphigus vulgaris
Cyclophos-phamide	It has marked effect on B cells and humoral immunity	Neutropenia Alopecia Raised transaminases Thrombocytopenia Secondary sterility[7] GI disturbances	Advantages: Inexpensive Oral administration Disadvantages: Potential risk of hemorrhagic cystitis and cancer of bladder	Systemic lupus erythematosus Multiple myeloma Pemphigus vulgaris in combination with vincristine, prednisolone and doxorubicin in non-Hodgkins lymphoma[8]
Glucocorticoids	Immunosuppression of both B and T cells; suppresses cell-mediated immunity	Diabetes Osteoporosis Adrenal suppression Peptic ulceration Gain in weight Increased susceptibility to infections Mood changes	Advantages: Effective Rapid onset Oral administration Inexpensive Disadvantages: Side effect profile	Anti-inflammatory Systemic lupus erythematosus Steven Johnsons syndrome Oral lichen planus

use of drugs for deliberately suppressing it appears odd at first sight. However, according to the present concept, the ability of the body to recognize self from nonself or foreign, which is the basis of immunity, is liable to cause disorders due to failure to recognize and tolerate antigens produced by its own tissues.

Mechanism of Action of Immunosuppressive Drugs

Generation of humoral and cell-mediated immune response and sites of action of immunosuppressant drugs (Fig. 1). The antigen (Ag) is processed by macrophages or other antigen presenting cells (APC), coupled with class II major histocompatibility complex (MHC) and presented to the CD4 helper cell which are activated by interleukin-I (IL-I), proliferate and secrete cytokines—these in turn promote proliferation and differentiation of antigen activated B cells into antibody (Ab) secreting plasma cells. Antibodies finally bind and inactivate the antigen.

In cell-mediated immunity—foreign antigen is processed and presented to CD4 helper T cells which elaborate IL-2 and other cytokines that in turn stimulate proliferation and maturation of precursor cytotoxic lymphocytes (CTL) that have been activated by antigen presented with class I MHC.

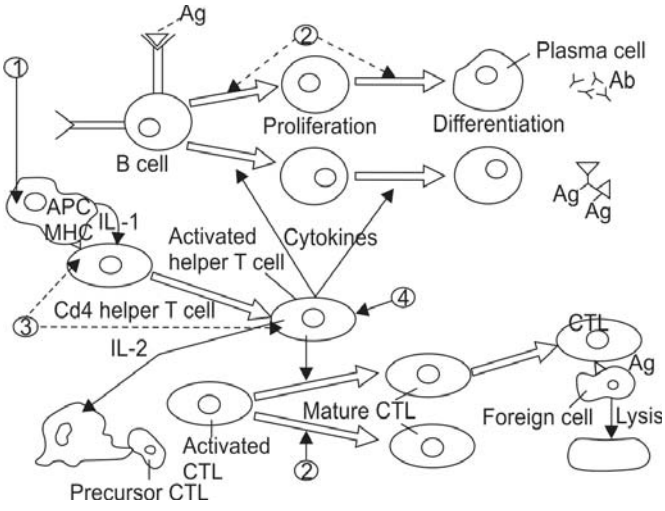

Fig. 1: Mechanism of action of immunosuppressive drugs *(Courtesy*: Tripathi KD: Essentials of Dental Pharmacology; 305)

The mature CTL (Killer cells) recognize cells carrying the antigen and lyse them.

1. Glucocorticoids inhibit MHC expression and IL-1, IL-2, IL-6 production so that helper T cells are not activated.
2. Cytotoxic drugs block proliferation and differentiation of T and B cells.
3. Cyclosporine and tacrolimus inhibit antigen stimulated activation and proliferation of helper T cells as well as expression of IL-2 and other cytokines by them.
4. Antibodies like muromonab CD3, antithymocyte globulin specific bind to helper T cells, prevent their response and deplete them.

Immunostimulants

The use of a variety of agents to enhance immunological and nonspecific host defences and thus to modify the

Table 3: Immunostimulants

Drugs	*Mechanism of action*	*Side effects*	*Advantages/ disadvantages*	*Other uses*
Thalidomide	It inhibits the synthesis of tumor necrosis factor-α (TNF-α) by activated monocytes 16—the mRNA becomes less stable	Contraindicated in women with child-bearing potential[9]	Advantages: Oral administration inexpensive	Multiple myeloma Recurrent aphthous stomatitis HIV associated aphthae Behcet's disease Systemic lupus erythematosus Oral lichen planus
Levamisole	Restores depressed immune function of B cells, T cells, Monocytes, Macrophages Levamisole ↓ Thymopoietin tertiary structure ↓ Stimulation of neutrophils, lymphocytes and macrophages ↓ Stimulation of T cells and phagocytosis ↓ Stimulation of immune system	GI disturbances Headache Dizziness Insomnia Thrombocytopenia Granulocytopenia Sores in the mouth and lip—an allergic reaction (including difficulty in breathing; closing of the throat; swelling of the lips, tongue, face or hives)	Advantages: Inexpensive Disadvantages: Side effect profile	Recurrent aphthous stomatitis Recurrent herpes infections Oral lichen planus Pemphigus vulgaris Erythema multiforme Refractory oral candidiasis
Recombinant cytokines—interferons and IL-2	Bind to cell surface receptors—initiate intracellular events Enzyme induction Inhibition of cell proliferation Enhancement of immune activities Increased phagocytosis	Flu-like symptoms Hypotension Arrhythmia Depression Confusion	Disadvantage: Expensive	Hairy cell leukemia Malignant melanoma Kaposis sarcoma

defences favorably is an exciting development in immunopharmacology (Table 3).

There has been significant progress in the search for selective immunomodulation; the most significant advance in immunotherapy has been the reduction in systemic glucocorticoids exposure along with early or concomitant introduction of immunosuppressive and immunomodulatory adjuvants.

Cytotoxic and and antimetabolic agents act through the inhibition and/or interruption of cell cycle. These drugs are used to treat serious, life threatening and recalcitrant diseases of the head, neck and face region.

Immunomodulators have a low therapeutic index (narrow window between the toxic and therapeutic range) and intra- and interindividual variation of the pharmacokinetics of these agents. These obstacles are usually overcomed by precise drug dosing (ideal/lean body weight and body surface area) as well as close monitoring of drug levels (parent and metabolite serum peak and trough levels) and organ toxicity.[10]

DISCUSSION

The growth of clinical immunology has uncovered increasing number of diseases that are due to eccentric immune responses. This has resulted in a search for drugs capable of restyling these unwanted responses. Over the past two decades, considerable progress has been made in identifying a group of compounds capable of modulating immune responses. Experience with immunomodulators in controlled clinical trial is currently limited, but many of these are effective for the treatment of malignant, infectious and immunologic disorders. However, since our understanding of the complex role of such agents in the immune system is still incomplete, the rational design of clinical studies remains a significant challenge. The eventual goal in this area is to develop specific immunomodulation or tolerance directed only at the immune response to selected antigens. This currently remains an elusive goal. Future research should likely focus on molecular and gene level mechanism to achieve the goal.

CONCLUSION

Topical corticosteroids have always been the mainstay therapy for malignant, immunological and infectious disorders since their introduction decades ago. Unfortunately, they are associated with the aftermaths. In recent years, with the debutante of immunomodulators, a collateral therapy for corticosteroids has come into materialization which has aided in the 'steroid-sparing effects'.

Thus, we as oral diagnosticians should encourage the use of these supplementary drugs so as to curb the monopoly of steroids and contribute toward the betterment of mankind.

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