Immunosuppressants

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Abstract- **Immunosuppressant is a class of medicine that inhibit or decrease the intensity of the immune response in the body. Most of these medications are used to allow the body less likely to resist a transplanted organ .In solid organ transplanted organ. In solid organ transplantation immunosuppressive agents are needed for the activation of early -stage immunosuppression, the management of organ rejection. The emergence of novel agent and improvement in immune suppression regimens after transplantation are significant factor leading to this progress .However, these drugs also increase the risk of infection , cancers and specific adverse side effects specific to each agent in patients particularly in pregnant women and fertility issues. Corona virus disease being hot topic of debate is has given positive outcome to immunosuppressive drug how ever need more attention I future. Transplant centres across the utilize multiple immunosuppression protocol's nevertheless , each patient can require an individually formulated immunosuppression regimen to manage the advantages and possible damage of treatment thus eliminating the likelihood of the primary disease recurrence.**

Keywords: **Immunosuppression, immunosuppressants, Calcineurin Inhibitors.**

INTRODUCTION:

Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Some portions of the immune system itself have immunosuppressive effects on other parts of the immune system, and immunosuppression may occur as an adverse reaction to treatment of other conditions. Immunosuppressants are used to control severe manifestations of allergic, autoimmune and transplant-related diseases. Some drugs have a diffuse effect on the immune system while others have specific targets. Drugs with diffuse effects are more likely to cause damaging adverse effects, but the effectiveness of the more specific drugs may be reduced if their action can be bypassed by alternative metabolic pathways. Treatment protocols therefore frequently use drug combinations to minimize adverse effects and to prevent resistance to treatment. Cortisone was the first immunosuppressant identified, but its wide range of side effects limited its use. The more specific azathioprine was identified in 1959, but it was the discovery of cyclosporine in 1970 that allowed for significant expansion of kidney transplantation to less well-matched donor-recipient pairs as well as broad application of liver transplantation, lung transplantation, pancreas transplantation, and heart transplantation. Some immunosuppressants act through immune depletion of effector cells, while others are predominantly immunomodulatory, affecting the activity of cells, usually through cytokine inhibition. Immunosuppressive drugs can be classified into five groups:

- Glucocorticoids
- Cytostatic
- Antibodies
- Drugs acting on Immunophilins
- Other drugs

GLUCOCORTICOIDS:

Corticosteroids are the mainstay of most immunosuppressive regimens in both the induction and maintenance phases. In high intravenous pulse doses (methylprednisolone 250–1000 mg daily for 1–3 days) they are directly lymphocytoxic. In smaller doses, they are immunosuppressive and anti-inflammatory by limiting cytokine production. The required dose and duration of treatment therefore tends to be disease specific. Some diseases, for example asthma, respond to a short course which can be abruptly stopped, but most rheumatic diseases require the dose to be very slowly tapered over months, especially when single figure milligram doses of prednisone are reached.

A. Immunosuppressive mechanism:

Glucocorticoids suppress the cell-mediated immunity. They act by inhibiting genes that code for the cytokines IL-1, IL-2, IL-3, IL-4, IL-5, IL6, IL-8 and TNF-γ, the most important of which is the IL-2. Smaller cytokine production reduces the T cell proliferation. Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and of IL-2 receptors. This diminishes both B cell clone expansion and antibody synthesis.

a. Alkylating agents:

The alkylating agents used in immunotherapy are nitrogen mustards (cyclophosphamide), nitrosoureas, platinum compounds and others. Cyclophosphamide is probably the most potent immunosuppressive compound.

Antimetabolites :

interfere with the synthesis of nucleic acids. These include: folic acid analogues, such as methotrexate; purine analogues such as azathioprine and mercaptopurine pyrimidine analogues; protein synthesis inhibitors. Methotrexate is a folic acid analogue. It binds dihydrofolate reductase and prevents synthesis of tetrahydrofolate. It is used in the treatment of autoimmune diseases (for example rheumatoid arthritis) and in transplantations.

Cytotoxic antibiotics:

Among these, dactinomycin is the most important. It is used in kidney transplantations. Other cytotoxic antibiotics are anthracyclines, mitomycin C, bleomycin, mithramycin.

CYTOSTATICS:

Cytostatic inhibit cell division. In immunotherapy, they are used in smaller doses than in the treatment of malignant diseases. They affect the proliferation of both T cells and B cells. Due to their highest effectiveness, purine analogues are most frequently administered. It includes the following: Alkylating agents; Antimetabolites and Cytotoxic antibiotics.[1]

DRUGS ACTING ON IMMUNOPHILINS:

a Cyclosporin:

Together with tacrolimus, cyclosporin is a calcineurin inhibitor. It has been in use since1983 and is one of the most widely used immunosuppressive drugs. It is a fungal peptide, composed of 11 amino acids. Cyclosporin is thought to bind to the cytosolic protein cyclophilin, of immunocompetent lymphocytes, especially T-lymphocytes.

b. Tacrolimus:

Tacrolimus is a fungal product . It is a macrolide lactone and acts by inhibiting calcineurin. The drug is used particularly in the liver and kidney transplantations, although in some clinics it is used in heart, lung and heart/lung transplants.

b. Mycophenolate mofetil:

Since it was introduced into Australia in 1996 mycophenolate mofetil has largely replaced azathioprine in organ transplantation. One advantage over azathioprine is that allopurinol can be used for gout prophylaxis without the need to reduce the dose of mycophenolate.[2]

OTHER DRUGS:

a. Interferons

Interferons IFN-β suppresses the production of Th1 cytokines and the activation of monocytes. It is used to slow down the progression of multiple sclerosis. IFN-γ is able to trigger lymphocytic apoptosis.

b. Opioids:

Prolonged use of opioids may cause immunosuppression of both innate and adaptive immunity. Decrease in proliferation as well as immune function has been observed in macrophages as well as lymphocytes. It is thought that these effects are mediated by opioid receptors expressed on the surface of these immune cells.

c .TNF binding proteins

A TNF-α (tumor necrosis factor alpha) binding protein is a monoclonal antibody or a circulating receptor such as infliximab, etanercept , or adalimumab, that binds to TNF-α and prevent it from inducing the synthesis of IL-1 and IL-6 and the adhesion of lymphocyte activating molecules. They are used in the treatment of rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and psoriasis. F or the effects of TNF are also suppressed by various natural compounds, including curcumin, and catechins.[3]

d. Mycophenolate:

Mycophenolic acid acts as a non-competitive, selective and reversible inhibitor of inosine monophosphate dehydrogenase, which is a key enzyme in the de novo guanosine nucleotide synthesis. In contrast to other human cell types, lymphocytes B and T are very dependent on this process.

c. Small biological agents:

FTY720 is a new synthetic immunosuppressant, currently in phase 3 of clinical trials. It increases the expression or changes the function of certain adhesion molecules (α4/β7 integrin) in lymphocytes, so they accumulate in the lymphatic tissue, and their number in the circulation is diminished. In this respect, it differs from all other known immunosuppressants.[4]

The following is a list of conditions in which 'Immunosuppressive drugs' are used:

1. Arteritis
2. Autoimmune diseases
3. Behcet's Disease
4. Chronic Inflammatory Demyelinating Polyneuropathy
5. Collagenous Colitis
6. Crohn's disease
7. Dermatomyositis
8. Eczema
9. Endocarditis
10. Glomerulonephritis
11. Goodpasture syndrome
12. Lupus
13. Myasthenia Gravis
14. Pemphigus [5]

Empiricism vs controlled:

trials Many protocols have evolved empirically from an understanding of the putative immune mechanisms operating in a particular disease. Sometimes the protocols were derived from what had been seen to work in conditions with apparently similar immunopathology. Randomised controlled trials of immunosuppressive protocols are available in the more common conditions such as rheumatoid arthritis or organ transplantation, but as new drugs emerge, the combinations for comparison become bewildering.

Choosing Immunosuppressive Regimens:

In order to make sound judgements when choosing a treatment protocol, the clinician has to consider the clinical trial evidence and then decide:

- The natural history of the untreated disease
- Is the disease multiphasic or 'single shot'
- The extent and severity of the disease in this particular patient
- Is the affected organ beyond recovery?
- The likelihood of relapse
- The ability to monitor disease parameters long term.[6]

MANAGING AND MONITORING PATIENTS TAKING IMMUNOSUPPRESSANTS :

Patients need to be under constant surveillance, usually by a partnership between the specialist and the general practitioner. Frequency of visits depends on perceived level of risk, but typical parameters to monitor are summarised in Patients may need prophylaxis against the adverse effects of their treatment . Therapeutic drug monitoring is available now for a number of drugs, for example cyclosporin, tacrolimus, sirolimus and mycophenolate.

Immunosuppressive drugs in some special cases:

Fertility and pregnancy

In most cases, especially after the first year of allogeneic organ transplantation, immunosuppression severity decreases with time. The eradication of diseased cells by chemotherapy is often followed by allogenic hematopoietic stem -cell transplantation. There is a dose -dependent reduction in testosterone plasma concentration, arises in gonadotrophins and in an improvement in spermatogenesis .[7]

Corona virus disease :

In order to inhibit and manage the hyper inflammatory process of COVID -19,it is speculated that immunosuppressive medications may be used. This medication , however, also suppress the host immune response to the virus. Thus, in earlier phases of COVID-19 patient is undergoing significant debates. Corticosteroids have a bord variety of anti-inflammatory and immunomodulatory properties, including suppression of pro- inflammatory cytokine production , reduction of the trafficking of leukocytes and activation of t- lymphocyte apoptosis. [8]

TABLE:1 Small molecule immunosuppressant drugs in current use

Class of drug	Generic name	Potential clinical uses	Drug monitoring	Main adverse effects
Immunophilin-binding drugs: Calcineurin inhibitors	cyclosporin	Organ transplants, nephrotic syndrome, atopic eczema, rheumatoid arthritis	TDM(C_0orC_2)creatinine inpotassium ,magnesium glucose, lipids	nephrotoxicity, hypertension, tremor, hirsutism, gum hypertrophy, diabetes,

				haemolytic uraemic syndrome
	tacrolimus	organ transplants	TDM(C0), creatinine, potassium, magnesium, glucose, lipids	as for cyclosporin but more tremor, diabetes, less hypertension and fewer cosmetic effects
Mammalian target of rapamycin (mTOR) inhibitor	sirolimus everolimus	organ transplants	TDM(C0), lipids, FBC, UA	delayed wound healing, mouth ulcers, acne, pancytopenia, hyperlipidaemia, interstitial pneumonitis, peripheral oedema, proteinuria
Inhibitors of nucleotide synthesis: Purine synthesis inhibitors	mycophenolate mofetil mycophenolic acid	organ transplants, vasculitides, SLE	TDM not widely used, FBC	diarrhoea, dyspepsia, neutropenia, anaemia, viral infections
Purine analogue	azathioprine	Organ transplant , rheumatoid arthritis, SLE , inflammatory bowel disease	FBC , LEFTs	Neutropenia macrocytosis, liver dysfunction, skin cancers.

Prognosis and unresolved questions:
In the 21st century, immunosuppressive drugs are indicated in many different diseases due to their efficacy but also due to a better understanding of their mechanisms of action and their side effects. This efficacy has enabled improvement of underlying diseases, making parenthood an option in some young patients who previously had definitive life-threatening conditions[9]

CONCLUSION:
Advances in our understanding of the immune aetiology of many debilitating diseases have resulted in wider use of immunosuppressant drugs in common clinical practice. The last two decades have seen the development of several useful small molecule drugs but also a profusion of monoclonal antibodies targeting the immune system. Increasingly, primary care physicians are involved in the supervision of patients taking these drugs. This task has been made easier and safer by the establishment of therapeutic targets for drug monitoring and the obligatory use of prophylactic drugs to prevent common adverse effects.

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