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Immunosuppressants: A Review

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Advances in immunosuppressants over the past decade have resulted in dramatic improvements in short- and long-term outcomes in organ transplantation as well as a decreased incidence of acute rejection. However, immunosuppressive drugs need to be given long term, lack specificity, and are accompanied by adverse metabolic derangements, toxicities, the risk of infection and cancer, and a myriad of other side effects. Further, they fail to prevent and control chronic rejection. This review will outline a number of immunosuppressive agents that are currently being explored in experimental and clinical transplantation. These include biologic agents that have more specificity and selectivity, and are aimed at T-cell depletion, blockade of costimulation, adhesion markers, or at novel targets.

Keyword: Immunosuppression, Calcineurin Inhibitors, Corticosteroids, Transplantation.

1. INTRODUCTION: Immunosuppression involves an act that reduces the activation or efficacy of the immune system. Some portions of the immune system itself have immuno-suppressive 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. Although protocols are essential to allow scientific evaluation, the clinician must be prepared to tailor treatment based on the ongoing assessment of drug effects, disease activity and the robustness of the individual patient.

Deliberately induced immunosuppression is generally done to prevent the body from rejecting an organ transplant or for the treatment of auto-immune diseases such as rheumatoid arthritis or Crohn's disease. This is typically done using drugs, but may involve surgery (splenectomy), plasmapharesis, or radiation. Many of the currently available immunosuppressants were developed for use in oncology or transplantation. As this treatment is potentially life-saving desperate measures can be justified. However,

there are now over 80 autoimmune diseases and several common allergic conditions in which immunosuppressants could play a role although they may not be life-saving. Clinically they are used to:

- Prevent the rejection of transplanted organs and tissues (e.g. bone marrow, heart, kidney, liver)
- Treatment of autoimmune diseases or diseases that are most likely of autoimmune origin (e.g. rheumatoid arthritis, myasthenia gravis, systemic lupus erythematosus, Crohn's disease, and ulcerative colitis).
- Treatment of some other non-autoimmune inflammatory diseases (eg. long term Allergic Asthma control).

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 immunodepletion 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:

I. Glucocorticoids
II. Cytostatics
III. Antibodies
IV. Drugs acting on Immunophilins
V. Other drugs

2. 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 lymphocytotoxic. 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. Abrupt cessation runs the risk not only of relapse of disease, but also hypoadrenocorticism. (Adrenal suppression can be confirmed by a one-hour synthetic ACTH stimulation test if there is clinical concern.) In the withdrawal phase, non-specific polyarthralgias and myalgias are common, but generally respond to a small dose increment followed by a renewed, slower taper.

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, IL-6, 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. Second-line drugs, usually antiproliferative drugs such as azathioprine, mycophenolate or methotrexate, may have a steroid-sparing effect in the maintenance phase of treatment. However, they also have their own toxicities. Patients prescribed corticosteroids should be told to expect the common early adverse effects, such as sweatiness, hoarse voice, loss of diurnal sleep patterns, and appetite stimulation. Rarely, more serious acute psychiatric disturbances are seen such as agitation, aggression or psychosis. Long-term, and less reversible, adverse effects include Cushingoid appearance, proximal myopathy, hypertension, hyperlipidaemia, diabetes, cataract formation, peptic ulceration, osteopenia and aseptic necrosis of bone.

3. CYTOSTATICS

Cytostatics 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 analogs are most frequently administered. It includes the following: Alkylating agents; Antimetabolites and Cytotoxic antibiotics.

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. In small doses, it is very efficient in the therapy of systemic lupus erythematosus, autoimmune hemolytic anemias, Wegener's granulomatosis and other immune diseases. High doses cause pancytopenia and hemorrhagic cystitis.

b. Antimetabolites

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. Azathioprine, is the main immunosuppressive cytotoxic substance. It is extensively used to control transplant rejection reactions. It is nonenzymatically cleaved to mercaptopurine that acts as a purine analogue and an inhibitor of DNA synthesis. Mercaptopurine itself can also be administered directly. By preventing the clonal expansion of lymphocytes in the induction phase of the immune response, it affects both the cell and the humoral immunity. It is also efficient in the treatment of autoimmune diseases.

c. Cytotoxic antibiotics

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

4. ANTIBODIES

Antibodies are used as a quick and potent immunosuppression method to prevent the acute rejection reaction. They are of two types: Polyclonal antibodies & Monoclonal antibodies

a. Polyclonal antibodies

Polyclonal antibodies inhibit T lymphocytes and cause their lysis, which is both complement mediated cytolysis and cell-mediated opsonization followed by removal of reticuloendothelial cells from the circulation in the spleen and liver. In this way, polyclonal antibodies inhibit cell-mediated immune reactions, including graft rejection, delayed hypersensitivity (i.e. tuberculin skin reaction), and the graft-versus-host disease (GVHD), but influence thymus-dependent antibody production. Polyclonal antibodies affect all lymphocytes and cause general immunosuppression possibly leading to post-transplant lymphoproliferative disorders (PTLD) or serious infections, especially by cytomegalovirus. To reduce these risks, treatment is provided in a hospital where adequate isolation from infection is available. They are usually administered for five days intravenously in the appropriate quantity. Patients stay in the hospital as long as three weeks to give the immune system time to recover to a point where there is no longer a risk of serum sickness.

Because of a high immunogenicity of polyclonal antibodies, almost all patients have an acute reaction to the treatment. It is characterized by fever, rigor episodes and even anaphylaxis. Later during the treatment, some patients develop serum sickness or immune complex glomerulonephritis. Serum sickness arises seven to fourteen days after the therapy has begun. The patient suffers from fever, joint pain and erythema that can be soothed with the use of steroids and analgesics. Urticaria (hives) can also be present. It is possible to diminish their toxicity

by using highly purified serum fractions and intravenous administration in the combination with other immunosuppressants, for example calcineurin inhibitors, cytostatics and cortisteroids. The most frequent combination is to simultaneously use antibodies and cyclosporine. Patients gradually develop a strong immune response to these drugs, reducing or eliminating their effectiveness.

b. Monoclonal antibodies

Monoclonal antibodies are directed towards exactly defined antigens. Therefore, they cause fewer side effects. Especially significant are the IL-2 receptor (CD25) and CD3 directed antibodies. They are used to prevent the rejection of transplanted organs, but also to track changes in the lymphocyte subpopulations. It is reasonable to expect similar new drugs in the future. More recently, hybridoma technology has produced a plethora of monoclonal antibodies against molecules expressed by human immune effector cells. T-lymphocyte depleting antibodies such as muromonab-CD3 have been widely used to prevent or treat acute rejection of organ transplants. The main drawback is a 'cytokine storm' reaction to the first dose, which can cause life-threatening pulmonary oedema. Basiliximab and daclizumab are monoclonal antibodies against the interleukin-2 receptor (CD25). They are used as induction drugs in transplantation as they significantly reduce the acute rejection rate, with little or no increase in morbidity. They are not yet significantly used in autoimmune diseases.

The anti-B cell antibody (anti-CD20), rituximab, is licensed for use against B-cell lymphomata, but there are now published anecdotal reports of its effectiveness in 29 different autoimmune diseases.7 Randomised controlled trials are proceeding in systemic lupus erythematosus, rheumatoid arthritis, dermatomyositis, antineutrophil cytoplasmic antibody (ANCA)-positive vasculitis and in renal transplantation of highly sensitised recipients.

A new monoclonal antibody, alemtuzumab, is directed against a surface molecule (CD54), which is widely distributed on lymphocytes, macrophages and dendritic cells, thereby causing severe and long-lasting depletion of these cell lines. As a result, the risk of serious infection is increased. The use of this antibody is cautiously making the transition from immunoprophylaxis in transplant recipients to a wider use in immune diseases. Two monoclonal antibodies against tumour necrosis factor, infliximab and adalimumab, and etanercept which prevents tumour necrosis factor binding to its receptor, are licensed for use in rheumatoid arthritis. They are also being used in ankylosing spondylitis, psoriatic arthritis and inflammatory bowel disease.9 Infusion reactions are common. These are again of two types: T-cell receptor directed antibodies & IL-2 receptor directed antibodies.

c. T-cell receptor directed antibodies

OKT3 (R) is presently the only approved anti-CD3 antibody. It is a mouse anti-CD3 monoclonal antibody of the IgG2a type that prevents T-cell activation and proliferation by binding the T-cell receptor complex present on all differentiated T cells. As such, it is one of the most potent immunosuppressive substances and is clinically used to control the steroid and/or polyclonal antibodies resistant acute rejection episodes. For acting more specifically than polyclonal antibodies, it is also used preventively in transplantations. Presently, the OKT3's action mechanism is not yet sufficiently understood. It is known that the molecule binds TCR/CD3, the T-cell receptor complex. During the first few administrations, this binding non-specifically activates T cells, leading to a serious syndrome 30 to 60 minutes later. It is characterized by fever, myalgia, headache and artralgia. In some cases, it progresses to a life-threatening reaction of the cardiovascular system and the central nervous system needing a lengthy therapy. Past this period, CD3 (R) blocks the TCR - antigen binding and causes conformation change or the removal of the entire TCR3/CD3 from the T-cell surface. This lowers the number of T cells, perhaps by sensitising them for the uptake by the reticular epithelial cells. The cross-binding of CD3 molecules also activates an intracellular

signal, causing the T cells' anergy or apoptosis, unless they receive another signal through a costimulatory molecule. CD3 antibodies also shift the balance from Th1 to Th2 cells.

Deciding whether to use OKT3(R) in the treatment, it is therefore necessary not only to consider its great effectiveness, but also its toxic side effects: the risk of excessive immunosuppression and the risk that the patient develops neutralizing antibodies against the drug, making it inefficacious. Although CD3(R) antibodies act more specifically than polyclonal antibodies, they lower the cell-mediated immunity significantly, predisposing the patient to opportunistic infections and malignancies
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d. IL-2 receptor directed antibodies
Interleukin-2 is an important immune system regulator necessary for the clone expansion and survival of activated lymphocytes T. Its effects are mediated by the trimer cell surface receptor IL-2a, consisting of the, α, β and γ chains. The IL-2a (CD25, T-cell activation antigen, TAC) is expressed only by the already activated T lymphocytes. Therefore, it is of special significance to the selective immunosuppressive treatment and the research has been focused on the development of effective and safe anti-IL-2 antibodies. By the use of the recombinant gene technology, the mouse anti-Tac antibodies have been modified leading to the presentation of two himeric mouse/human anti-Tac antibodies in the year 1998: basiliximab (Simulect (R)) and daclizumab (Zenapax (R)). These drugs act by binding the IL-2a receptor's α chain, preventing the IL-2 induced clonal expansion of activated lymphocytes and shortening their survival. They are used in the prophylaxis of the acute organ rejection after the bilateral kidney transplantation, both being similarly effective and with only few side effects.

5. DRUGS ACTING ON IMMUNOPHILINS

a. Cyclosporin
Together with tacrolimus, cyclosporin is a calcineurin inhibitor. It has been in use since 1983 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 (an immunophilin) of immunocompetent lymphocytes, especially T-lymphocytes. This complex of cyclosporin and cyclophilin inhibits calcineurin, which under normal circumstances induces the transcription of interleukin-2. The drug also inhibits lymphokine production and interleukin release, leading to a reduced function of effector T-cells. Cyclosporin is used in the treatment of acute rejection reactions, but has been increasingly substituted with newer immunosuppressants, as it is nephrotoxic.

b. Tacrolimus
Tacrolimus is a fungal product (Streptomyces tsukubaensis). 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. It binds to an immunophilin, followed by the binding of the complex to calcineurin and the inhibition of its phosphatase activity. In this way, it prevents the passage of G0 into G1 phase. Tacrolimus is more potent than cyclosporin and has less pronounced side effects.

c. Sirolimus
Sirolimus is a macrolide lactone, produced by the actinomycetes Streptomyces hygroscopicus. It is used to prevent rejection reactions. Although it is a structural analogue of tacrolimus, it acts somewhat differently and has different side effects.
Contrary to cyclosporine and tacrolimus that affect the first phase of the T lymphocyte activation, sirolimus affects the second one, namely the signal transduction and their clonal proliferation. It binds to the same receptor (immunophilin) as tacrolimus, however the produced complex does not inhibit calcineurin, but another protein. Therefore, sirolimus acts synergistically with cyclosporine and in combination with other immunosuppressants, has

few side effects. Indirectly it inhibits several T lymphocyte kinases and phosphatases, preventing the transmission of signal into their activity and the transition of the cell cycle from G1 to S phase. Similarly, it prevents the B cell differentiation to the plasma cells, which lowers the quantity of IgM, IgG and IgA antibodies produced. It acts as an immunoregulatory agent, and is also active against tumors that involve the PI3K/AKT/mTOR pathway.

d. 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. Possibly because of its anti-B cell properties mycophenolate seems particularly effective in severe forms of systemic lupus erythematosus. It is also gaining favour as a steroid-sparing drug in the maintenance phase of a number of immune disorders, particularly the vasculitides. The main adverse effects are haematological and gastrointestinal. On higher doses a third of patients will develop diarrhoea. An enteric-coated formulation of mycophenolate has been developed to try and reduce gastrointestinal adverse effects.

6. OTHER DRUGS

a. 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 (Remicade®), etanercept (Enbrel®), or adalimumab (Humira®) 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 (an ingredient in turmeric) and catechins (in green tea). These drugs may raise the risk of contracting tuberculosis or inducing a latent infection to become active. Infliximab and adalimumab have label warnings stating that patients should be evaluated for latent TB infection and treatment should be initiated prior to starting therapy with them.

d. Mycophenolate

Mycophenolic acid acts as a non-competitive, selective and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), 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.

e. 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 (lymphatic nodes) and their number in the circulation is diminished. In this respect, it differs from all other known immunosuppressants.

The following is a lists 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
15. Polyarteritis nodosa
16. Reiter's syndrome
17. Rheumatoid arthritis
18. Schilder's Disease
19. Scleritis
20. Sjogren's Syndrome
21. Sympathetic ophthalmitis
22. Temporal arteritis
23. Thrombocytopenia
24. Transplants

f. Calcineurin inhibitors

Since the 1980s, calcineurin inhibitors have been the main contributors to the success of solid organ transplantation, especially kidneys. By blocking interleukin-2 synthesis, they prevent activation of T -lymphocytes and are therefore useful in disorders of cell-mediated immunity. Calcineurin inhibitors have a proven role in the prevention of acute cellular rejection of transplanted organs, in psoriasis and in nephrotic syndrome. They have been used in many other autoimmune conditions but have a diminishing role in rheumatoid arthritis. While they are good at maintaining autoimmune diseases in remission, withdrawal often leads to relapse. In solid organ transplantation, combinations of calcineurin inhibitors, mycophenolate mofetil and prednisone give better results than monotherapy. Ironically, calcineurin inhibitors are nephrotoxic and may contribute to   long-term renal failure, both in transplanted organs and normal kidneys. They also aggravate hypertension and hyperlipidaemia thereby inducing an unfavourable cardiovascular profile. There is also an increased risk of diabetes.

g. Immunosuppressants Use– Strategies and Protocols

Treatment protocols are designed to:
(a) Remove/suppress the predominant immune effectors and/or
(b) Resolve acute inflammation
(c) Prevent relapse.
To achieve (a) and (b), high doses are often used initially ('induction phase'). To achieve (c), lower doses of safer drugs are often chosen for the longer term ('maintenance phase').
Withdrawal of therapy is usually only considered after achieving clinical and laboratory evidence of sustained remission. Drugs are withdrawn gradually, one at a time and in the case of corticosteroids only after a long taper.

7. 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. Today's 'gold standard' treatment can be very quickly outdated, perhaps even before it has been optimised. Tailoring of immunotherapy to the individual is desirable, but this approach makes protocol comparisons difficult. Similarly, the disease being treated may be so pleomorphic that finding like populations to compare in trials becomes very difficult. For example, lupus nephritis has five distinct histological subtypes, each with their own prognosis.

8. 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:

- Is the aim to pre-empt an anticipated immune response (for example, after organ transplantation) or to suppress an established immune-mediated inflammation (for example, acute glomerulonephritis)?
- In the case of an immune disease, how much immunosuppression will be required and for how long (that is, an assessment of disease activity)? Consider:
  - The natural history of the untreated disease
  - Is the disease multiphasic (for example, polyarteritis nodosa) or 'single shot' (for example, microscopic polyangiitis)
  - 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

- Is this patient likely to withstand the treatment recommended (host fitness parameters)? Consider:
  - Age (older patients are easier to immunosuppress but have a greater risk of infection)
  - Sepsis risk
  - Cancer risk
  - Cardiovascular/diabetes risk
  - Presence of comorbidities
  - Patient compliance and availability for follow-up.

In choosing the dose and duration of immunosuppressive treatments, one must always weigh disease activity versus host fitness. For example, an elderly patient with perinuclear-ANCA positive microscopic polyangiitis, confined to the kidneys, with crescents in 10% of glomeruli, will not need as aggressive an approach as the same disease in a young patient, with 80% crescents, lung haemorrhage and mononeuritis multiplex.

9. 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 Table 3. Patients may need prophylaxis against the adverse effects of their treatment (Table 4). Therapeutic drug monitoring is available now for a number of drugs, for example cyclosporin, tacrolimus, sirolimus and mycophenolate. This allows for 'concentration-controlled' regimens. Some common drugs, for example corticosteroids, still have no good measure of individual bioavailability.

a. Infection risk

Immunosuppression increases susceptibility to infections which can become life-threatening in a matter of hours. At first, common bacterial infections of wounds, chest or urine predominate, but after 1–2 months of therapy opportunistic infections emerge, particularly herpes viruses, pneumocystis pneumonia, fungi and atypical mycobacteria. Vaccinations against influenza (injected) and pneumococcus are recommended in chronically immunosuppressed patients.[12]
They are safe and reasonably effective when given in the stable maintenance phase. In general, live attenuated virus vaccines, such as varicella or measles, should not be given to immunosuppressed patients (or to close family contacts).

b. Cancer risk

In patients taking immunosuppressants, early cancers are often viral induced. They include lymphoproliferative disorders and cervical cancer. In the long term, nearly all common cancers are increased, but particularly skin cancers. After 20 years of immunoprophylaxis following renal transplant, 80% of Australian patients will have developed skin cancer.

c. Precautions

Seeing a physician regularly while taking immunosuppressant drugs is important. These regular check-ups will allow the physician to make sure the drug is working as it should and to watch for unwanted side effects. These drugs are very powerful and can cause serious side effects, such as high blood pressure, kidney problems and liver problems. Some side effects may not show up until years after the medicine is used. Anyone who has been advised to take immunosuppressant drugs should thoroughly discuss the risks and benefits with the prescribing physician.

Immunosuppressant drugs lower a person's resistance to infection and can make infections harder to treat. The drugs can also increase the chance of uncontrolled bleeding. Anyone who has a serious infection or injury while taking immunosuppressant drugs should get prompt medical attention and should make sure that the treating physician knows about the immunosuppressant prescription. The prescribing physician should be immediately informed if signs of infection, such as fever or chills, cough or hoarseness, pain in the lower back or side, or painful or difficult urination, bruising or bleeding, blood in the urine, bloody or black, tarry stools occur. Other ways of preventing infection and injury include washing the hands frequently, avoiding sports in which injuries may occur, and being careful when using knives, razors, fingernail clippers or other sharp objects. Avoiding contact with people who have infections is also important. In addition, people who are taking or have been taking immunosuppressant drugs should not have immunizations, such as smallpox vaccinations, without checking with their physicians. Because of their low resistance to infection, people taking these drugs might get the disease that the vaccine is designed to prevent. People taking immunosuppressant drugs also should avoid contact with anyone who has taken the oral polio vaccine, as there is a chance the virus could be passed on to them. Other people living in their home should not take the oral polio vaccine. Immunosuppressant drugs may cause the gums to become tender and swollen or to bleed. If this happens, a physician or dentist should be notified. Regular brushing, flossing, cleaning and gum massage may help prevent this problem. A dentist can provide advice on how to clean the teeth and mouth without causing injury.

d. Special conditions
People who have certain medical conditions or who are taking certain other medicines may have problems if they take immunosuppressant drugs. Before taking these drugs, the prescribing physician should be informed about any of these conditions:

e. Allergies
Anyone who has had unusual reactions to immunosuppressant drugs in the past should let his or her physician know before taking the drugs again. The physician should also be told about any allergies to foods, dyes, preservatives, or other substances.

f. Pregnancy
Azathioprine may cause birth defects if used during pregnancy, or if either the male or female is using it at time of conception. Anyone taking this medicine should use a barrier method of birth control, such as a diaphragm or condoms. Birth control pills should not be used without a physician's approval. Women who become pregnant while taking this medicine should check with their physicians immediately. The medicine's effects have not been studied in humans during pregnancy. Women who are pregnant or who may become pregnant and who need to take this medicine should check with their physicians.

g. Breastfeeding
Immunosuppressant drugs pass into breast milk and may cause problems in nursing babies whose mothers take it. Breastfeeding is not recommended for women taking this medicine.

h. Other Medical Conditions

People who have certain medical conditions may have problems if they take immunosuppressant drugs. For example: People who have shingles (herpes zoster) or chickenpox, or who have recently been exposed to chickenpox, may develop severe disease in other parts of their bodies when they take these medicines; The medicine's effects may be greater in people with kidney disease or liver disease, because their bodies are slow to get rid of the medicine. The effects of oral forms of this medicine may be weakened in people with intestinal problems, because the medicine cannot be absorbed into the body.

Before using immunosuppressant drugs, people with these or other medical problems should make sure their physicians are aware of their conditions.

i. Use of Certain Medicines

Taking immunosuppressant drugs with certain other drugs may affect the way the drugs work or may increase the chance of side effects.

j. Side effects

Increased risk of infection is a common side effect of all the immunosuppressant drugs. The immune system protects the body from infections and when the immune system is suppressed, infections are more likely. Taking such antibiotics as co-trimoxazole prevents some of these infections. Immunosuppressant drugs are also associated with a slightly increased risk of cancer because the immune system also plays a role in protecting the body against some forms of cancer. For example, long-term use of immunosuppressant drugs carries an increased risk of developing skin cancer as a result of the combination of the drugs and exposure to sunlight.

Other side effects of immunosuppressant drugs are minor and usually go away as the body adjusts to the medicine. These include loss of appetite, nausea or vomiting, increased hair growth, and trembling or shaking of the hands. Medical attention is not necessary unless these side effects continue or cause problems.

k. Interactions

Immunosuppressant drugs may interact with other medicines. When this happens, the effects of one or both drugs may change or the risk of side effects may be greater. Other drugs may also have an adverse effect on immunosuppressant therapy. This is particularly important for patients taking cyclosporin or tacrolimus. For example, some drugs can cause the blood levels to rise, while others can cause the blood levels to fall and it is important to avoid such contraindicated combinations. Other examples are:

➢ The effects of azathioprine may be greater in people who take allopurinol, a medicine used to treat gout.

➢ A number of drugs, including female hormones (estrogens), male hormones (androgens), the antifungal drug ketoconazole (Nizoral), the ulcer drug cimetidine (Tagamet) and the erythromycins (used to treat infections), may increase the effects of cyclosporine.

➢ When sirolimus is taken at the same time as cyclosporin, the blood levels of sirolimus may be increased to a level where there are severe side effects. Although these two drugs are usually used together, the sirolimus should be taken four hours after the dose of cyclosporin.

➢ Tacrolimus is eliminated through the kidneys. When the drug is used with other drugs that may harm the kidneys, such as cyclosporin, the antibiotics gentamicin and amikacin, or the antifungal drug amphotericin B, blood levels of tacrolimus may be increased. Careful kidney monitoring is essential when tacrolimus is given with any drug that might cause kidney damage.

➢ The risk of cancer or infection may be greater when immunosuppressant drugs are combined with certain other drugs which also lower the body's ability to fight disease and infection. These drugs include corticosteroids such as prednisone; the anticancer drugs chlorambucil (Leukeran), cyclophosphamide (Cytoxan) and mercaptopurine (Purinethol); and the monoclonal antibody muromonab-CD3

(Orthoclone), which also is used to prevent transplanted organ rejection.

10. 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. Good clinical judgement, supported by laboratory investigations, is needed to differentiate the patients who are over-immunosuppressed (and therefore at risk of infections and cancer) from those experiencing relapse of their underlying disease.

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