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Review Article

IMMUNOMODULATORS: A PHARMACOLOGICAL REVIEW

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ABSTRACT

Immunology is one of the most rapidly developing areas of medical biotechnology research and has great promises with regard to the prevention and treatment of a wide range of disorders such as the inflammatory diseases of skin, gut, respiratory tract, joints and central organs. In addition, infectious diseases are now primarily considered immunological disorders, while neoplastic diseases and organ transplantation and several autoimmune diseases are involved in an immunosuppressive state. Immunomodulators are natural or synthetic substances that help regulate or normalize the immune system. Immunomodulators correct immune systems that are out of balance. Natural immunomodulators are less potent than prescription immunomodulators and also less likely to cause side effects. Prescription synthetic immunomodulator medications, such as azathioprine, 6-mercaptopurine, methotrexate, and mycophenolate mofetil, work by suppressing the immune system and decreasing inflammation in the digestive tract in people with inflammatory bowel disease, ulcerative colitis, and Crohn's disease. The benefits of immunomodulators stem from their ability to stimulate natural and adaptive defense mechanisms, such as cytokines, which enables the body to help itself. There are two types of immunomodulators: immunosuppressants and immunostimulants. Immunosuppressants are the agents which suppress the immune system and are used for the control of pathological immune response in autoimmune disease, graft rejection etc. Immunostimulants are the agents which are envisaged to enhance body's resistance against infections; they enhance the basal levels of immune response, and in individuals with impairment of immune response as immunotherapeutic agent. A number of disorders such as immunodeficiency state, autoimmune disease, cancer and viral infection can be treated with immunostimulants drugs. Immunomodulators are becoming a viable adjunct to established modalities offering a novel approach for the treatment of infectious disease in the coming decades of 21st century

Keywords: Immunomodulators, Antigen, Transplantation, Antibodies.

INTRODUCTION

Immunology is one of the most rapidly developing area of medical biotechnology research and has great promises with regard to the prevention and treatment of a wide range of disorders such as the inflammatory diseases of skin, gut, respiratory tract, joints and central organs. In addition infectious diseases are now primarily considered immunological disorders while neoplastic diseases, organ transplantation and several autoimmune diseases may involve in an immunosuppressive state [1]. The immune system is one of our most complex biological systems in the body. The basic role of the immune system is to distinguish self from non-self [2]. This non-self could be an infectious organism, a transplanted organ or an endogenous cell that can be mistaken as a foreign. The immune responses of the human body against any non-self are of two types: (a) innate (or natural or non-specific) and (b) adaptive (or acquired or specific) [3]. Both these responses have two components each, viz. cellular and humoral. Innate immunity lacks specificity as there is no involvement of memory cells. Acquired immunity on other hand is specifically adapted for the inducing pathogens and response improves with subsequent exposures to the same pathogen due to the presence of memory cell line. In the innate cellular immunity there is involvement of monocytes-macrophage system, while in innate humoral immunity there is activation of component system. On the other hand the cellular component of acquired immunity consists of T-lymphocytes while the humoral component of this immunity involves the role of B-lymphocytes. Normally in innate and acquired immune responses act in concerted manner to contain or eradicate infection. In some cases innate responses are enough to neutralise the offending agent. However in many other cases, certain cells of innate immune system, such as antigen presenting cells (APC), can also process the offending agent into smaller fragments which then activate adaptive immune system to neutralise or kill these pathogens. The elements formed in the blood are erythrocytes (RBC), leukocytes (WBC) and thrombocytes (platelets). The leukocytes are of two types: granulocytes (neutrophils, eosinophils and basophils) and agranulocytes (T-lymphocytes, B-lymphocytes and monocytes). The process by which blood cells are formed is called haemopoiesis. All such cells are involved in exerting immune response develops from pluripotent haemotopoietic stem cells which resides in bone marrow. These stem cell gives rise to lymphoid stem cell, trilineage myeloid stem cell, megakaryocytes (from platelets) and erythroblasts (from erythrocytes). The lymphoid stem cells through their progenitors, gives rise to mature lymphocytes (T-lymphocytes and B-lymphocytes) and natural killer cells (NK cells). T- and B-lymphocytes are involved in mediating adaptive immune responses while NK cells exert innate immune response along with mature cells originating from trilineage myeloid stem cells. When exposed to specific antigens, B-lymphocytes differentiate into antibody producing plasma cells in the bone marrow. Simultaneously, t-cells, under the influence of thymic hormones, migrate to the thymus and on appropriate stimulus by antigen presenting cells (APC) acquire T-cell receptor (TCR) and get differentiated to helper T-cells (with specific protein cluster of differentiation- CD4+) and cytotoxic T-cells (with specific protein cluster of differentiation- CD8+). The CD4+ (TH cell) subtypes of T-cells differentiate further outside the thymus into several phenotypes: TH1, TH2 and TH3 which are distinguished by the different cytokines (IL-2 and IFN-γ) they synthesize. TH1 T-cells produce cytokines that stimulate proliferation and differentiation of T-lymphocytes and NK cells. These cytokine play an important role in cell mediated immunity (CMI). TG2 T-cells release cytokine (IL-4, IL-5, IL-10 and IL-13) that stimulate B-lymphocytes production for humoral immunity. TH3 T-cells play an important role in resting phases of immune response and in the production of anti-inflammatory immunoglobin-A (IgA) antibodies that are important in secretory immunity [4].

The benefits of immunomodulators stem from their ability to stimulate natural and adaptive defense mechanisms, such as cytokines, which enables the body to help itself [5]. The natural immunomodulators act to strengthen weak immune systems and to moderate immune systems that are overactive. Plant sterols and sterolins are natural immunomodulators found in some raw fruits and vegetables and in the alga, spirulina. Spreads and yoghurt-type foods containing high levels of plant sterols are commonly to be found on sale as 'cholesterol-reducing' agents. These compounds are destroyed when vegetables and fruits are cooked. Other natural immunomodulators include *aloe vera, plumbago indica, aegle marmalos* [6], ginseng root, chamomile tea, reishi

mushroom extract, olive leaf extract, *N. sativa* oil, polysaccharides isolated from *Juniperus scopolorum*, *Isodon serra* extract, *ficus carica* leaf extract [7,8,9,10,11]. In children, immunomodulators are less likely to cause growth failure than corticosteroids. Topical immunomodulators are well tolerated even in infants [12]. Recent research carried out in Russia has identified extracts of certain Siberian plant species (Aconitum baikalense, Cirsium setosum and Saussurea controversa) as potent natural immunomodulators. The extracts are dissimilar chemically but have similar immune system enhancing effects. They have successfully been used for the treatment of benign and malignant tumors, antibiotic-resistant infections, allergies, polyarthrites, thyroid diseases, psoriasis and other pathologies which can be treated with medicines only with difficulty, if at all. The synthetic immunomodulator capsaicin-anandamide (hybrid arvanil) has been found to ameliorate symptoms in autoimmune encephalomyelitis in mice. The relevance of these findings suggests that arvanil and related compounds may offer benefits in the treatment of multiple sclerosis. A series of triptolide analogs have been successfully synthesized one of them is 5(R)-5-hydroxytriptolide showed low cytotoxicity and relatively high immunosuppressive activities as compaired with its parent compound triptolide [11,14]. Patent immunomodulator preparations containing naturally-derived ingredients include Immunoferon™, Licopid™, Biobran™, AHCC, Noxylane4™, Leucomeal™ and MGN.

Drugs used for Immunomodulation

All drugs which modify immune response generally categorized as immunomodulators. These can either function as:

1. Immunosuppressants
2. Immunostimulants.

Some of these can have both the properties depending on which component of immune response they affect. There is also an upcoming generation of immunosuppressants called tolerogens.

1. Immunosuppressant drugs

Table 1: Classification of Immunosuppressants

Sr. No.	Mechanism of Action	Examples
1.	Inhibitors of Lymphocyte Gene Expression	Glucocorticoids
2.	Inhibitors of Lymphocyte Signaling	
	a) Calcineurin Inhibitors	Cyclosporine, Tacrolimus
	b) mTOR Inhibitors	Sirolimus, Everolimus
3.	Cytotoxic Agents	
	a) Antimetabolites	Azathiprine, Mthotrexate, leflunomid. Cyclophosphamide
	b) Alkylating agents	
4.	Cytokine Inhibitors (Anticytokine-Antibodies)	
	a) TNF-α Inhibitors	Etanercept, Infliximab, Adalimumab
	b) IL-1 Inhibitors	Anakinra
	c) IL-2 Inhibtors	Daclizumab, Basiliximab
5.	Antibodies Against Specific Immune Cell Molecules	
	a) Polyclonal Antibodies	Antithymocyte Globulin (ATG)
	b) Monoclonal Antibodies	Alemutuzmab(AntiCD-52 Antibodies) Muromunab (Anti CD-3 Antibodies, OKT-3)
6.	Inhibitors of Immune Cell Adhesion	Efalizumab (LFA-1 Inhibitor)
7.	Tolerogens or Inhibitors of Immune Cell Costimulation	
8.	Miscellaneous	Rho (D) Immune Globulin

I. Inhibitors of Lymphocyte Gene Expression to Reduce Inflammatory Response-

e.g. Glucocorticoids:

- Mechanism of Action**:**

Multiple mechanisms are involved in the suppression of inflammation by glucocorticoids. Glucocorticoids inhibit the production by multiple cells of factors that are critical in generating the inflammatory response. As a result there is decreased release of vasoactive and chemoattractive factors diminished secretion of lipolytic and proteolytic enzymes decreased extravasation of leukocytes to areas of injury and ultimately decreased fibrosis. Glucocorticoids can also reduce expression of proinflammatory cytokines such as COX-2 and NOS2. The influence of stressful conditions on immune defense mechanisms is well documented as is the contribution of the HPA axis to the stress response. Stresses such as injury, infection and disease result in the increased production of cytokines a network of signaling molecules that integrate actions of macrophages/monocytes, T lymphocytes and B lymphocytes in mounting immune responses. Among these cytokines interleukin (IL)-1, IL-6, and tumor necrosis factor-a (TNF-a) stimulate the HPA axis with IL-1 having the broadest range of actions. IL-1 stimulates the release of CRH by hypothalamic neurons, interacts directly with the pituitary to increase the release of ACTH and may directly stimulate the adrenal gland to produce glucocorticoids. Factors that are inhibited include components of the cytokine network, including interferon-g (IFN-g), granulocyte-macrophage colony-stimulating factor (GM-CSF), interleukins (IL-1, IL-2, IL-3, IL-6, IL-8, and IL-12), and TNF-a.

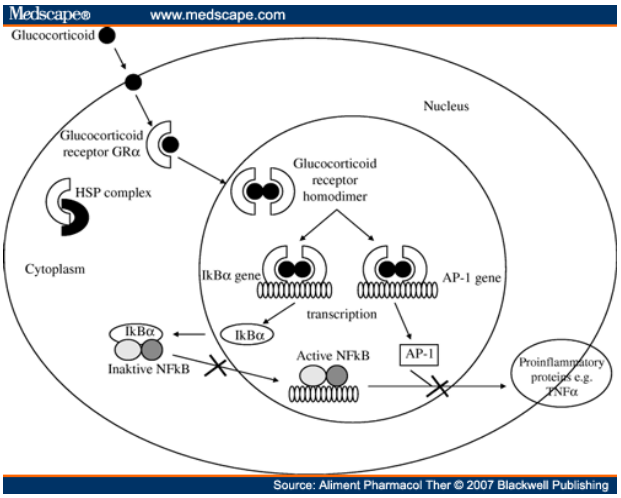

Fig. 1: Mechanism of Action of Glucocorticoids

- Therapeutic Uses**:**

Acute transplant rejection, graft-versus-host disease in bone-marrow transplantation, rheumatoid and other arthritides, systemic lupus erythematosus, systemic dermatomyositis, psoriasis and other skin conditions, asthma and other allergic disorders, inflammatory bowel disease, inflammatory ophthalmic diseases.

- Adverse Effects**:**

Growth retardation in children, avascular necrosis of bone, osteopenia, increased risk of infection, poor wound healing, cataracts, hyperglycemia, and hypertension [4,19,20,22].

II. Inhibitors of Lymphocyte Signaling to Prevent Immune Cell Activation and Proliferation-

a) Calcineurin Inhibitors-

Cyclosporine:

Cyclosporine (cyclosporin A), a cyclic polypeptide consisting of 11 amino acids is produced by the fungus species *Beauveria nivea*.

- Mechanism of Action**:**

Cyclosporine suppresses T-cell-dependent immune mechanisms such as those underlying transplant rejection and some forms of autoimmunity. It preferentially inhibits antigen-triggered signal transduction in T lymphocytes, blunting expression of many lymphokines including IL-2 and the expression of antiapoptotic proteins. Cyclosporine forms a complex with cyclophilin, a cytoplasmic receptor protein present in target cells. This complex binds to calcineurin, inhibiting Ca^{2+}-stimulated dephosphorylation of the cytosolic component of nuclear factor for activated T-cells (NFAT). When cytoplasmic NFAT is dephosphorylated and translocates to the nucleus and complexes with nuclear components required for complete T-cell activation including transactivation of IL-2 and other lymphokine genes. Calcineurin phosphatase activity is inhibited after physical interaction with the cyclosporine/cyclophilin complex. This prevents NFAT dephosphorylation such that NFAT does not enter the nucleus gene transcription is not activated and the T lymphocyte fails to respond to specific antigenic stimulation. Cyclosporine also increases expression of transforming growth factor-b (TGF-b), a potent inhibitor of IL-2-stimulated T-cell proliferation and generation of cytotoxic T lymphocytes (CTL).

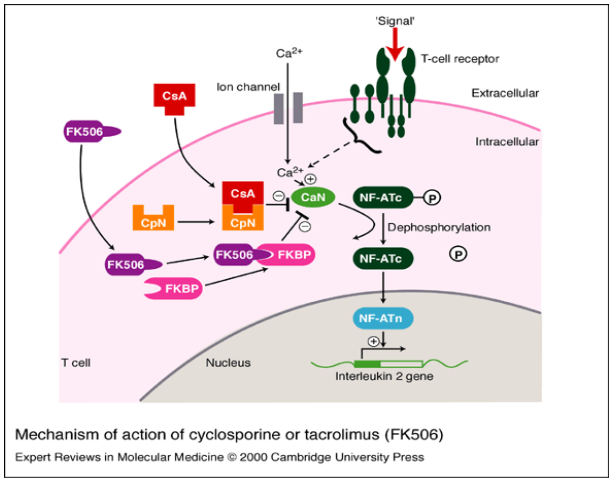

Fig. 2: Mechanism of Action of Cyclosporine or Tacrolimus

- Pharmacokinetics**:**

Cyclosporine can be given orally or I.V. Its oral bioavailability is low (about 30%). Food decreases its absorption. It is metabolized by CYP3A which may result in drug-drug interactions. Inactive metabolites are excreted mainly in bile and then in feces but minimally in urine. Plasma half life is about 24 hrs.

- Therapeutic Uses:

Kidney, liver, heart, and other organ transplantation, rheumatoid arthritis and psoriasis, early engraftment, extending kidney graft survival, cardiac and liver transplantation, Behcet's acute ocular syndrome, endogenous uveitis, atopic dermatitis.

- Adverse effects:

Renal dysfunction, tremor, hirsutism, hypertension, hyperlipidemia, gum hyperplasia, hyperuricemia, hyper-cholesterolemia, nephrotoxicity, hypertension, diabetogenic, Elevated LDL cholesterol [4,15,18,19,21,23].

Tacrolimus:

Tacrolimus (PROGRAF, FK506) is a macrolide antibiotic produced by *Streptomyces tsukubaensis*.

- Mechanism of Action**:** Like cyclosporine, tacrolimus inhibits T-cell activation by inhibiting calcineurin. Tacrolimus binds to an intracellular protein FK506-binding protein-12 (FKBP-12) an immunophilin structurally related to cyclophilin. A complex of tacrolimus-FKBP-12, Ca^{2+}, calmodulin, and calcineurin then forms, and calcineurin phosphatase activity is inhibited. As described for cyclosporine the inhibition of phosphatase activity prevents dephosphorylation and nuclear translocation of NFAT and inhibits T-cell activation.

- Pharmacokinetics:

Tacrolimus can be given orally or I.V. It is 99% metabolized in liver by CYP3A and has a plasma half life of 7-8 hrs.

- Therapeutic Uses:

Prophylaxis of solid-organ allograft rejection, kidney transplantation, pediatric liver transplantation.

- Adverse effects**:**

Nephrotoxicity, neurotoxicity (tremor, headache, motor disturbances and seizures), GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes [15,24,26].

b) Mammalian Target of Rapamycin (mTOR) Inhibitors:

Sirolimus:

Sirolimus (rapamycin; RAPAMUNE) is a macrocyclic lactone produced by *Streptomyces hygroscopicus.*

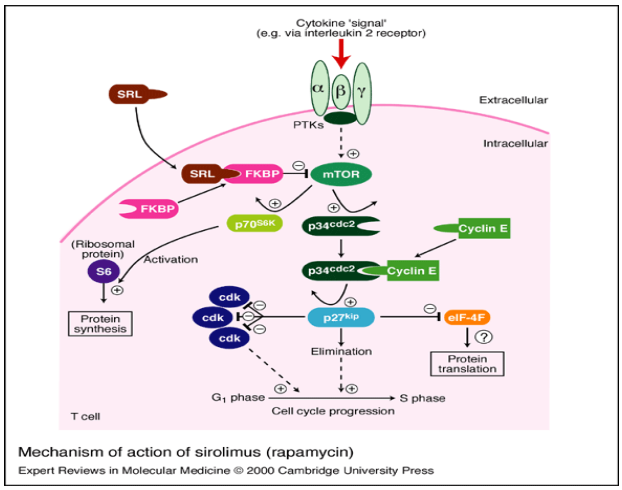

Fig. 3: Mechanism of action of Sirolimus

- Mechanism of Action**:**

Sirolimus inhibits T-lymphocyte activation and proliferation downstream of the IL-2 and other T-cell growth factor receptors. Sirolimus requires formation of a complex with an immunophilin in this case FKBP-12. However, the sirolimus-FKBP-12 complex does not affect calcineurin activity. It binds to and inhibits a protein kinase designated mammalian target of rapamycin (mTOR) which is a key enzyme in cell-cycle progression. Inhibition of mTOR blocks cell-cycle progression at the G_1 to S- phase transition.

- Pharmacokinetics**:**

Oral bioavailability is 15%. Fatty meal decreases its bioavailability. Protein binding is 40-45% mainly with albumin. It is extensively metabolized in liver by CYP3A4. Sirolimus is excreted 91% in feces and only 2.5% in urine. Plasma half life is 62 hrs.

- Therapeutic Uses:

Organ transplant inhibitor, graft rejection, incorporated into stents to inhibit local cell proliferation and blood vessel occlusion.

- Adverse Effects:

Dose-dependent increase in serum cholesterol and triglycerides, impaired renal function, prolong delayed graft function, Lymphocele, anemia, leukopenia [15,18,27].

III. Cytotoxic Agents to Reduce Lymphocyte Proliferation-

a) Antimetabolites

Azathioprine:

Azathioprine (IMURAN) is a purine antimetabolite. It is an imidazolyl derivative of 6-mercaptopurine.

- Mechanism of Action**:** Following exposure to nucleophiles such as glutathione, azathioprine is cleaved to 6-mercaptopurine, which in turn is converted to additional metabolites that inhibit de novo purine synthesis. 6-Thio-IMP, a fraudulent nucleotide, is converted to 6-thio-GMP and finally to 6-thio-GTP, which is incorporated into DNA. Cell proliferation is thereby inhibited impairing a variety of lymphocyte functions.

- Therapeutic Uses: Allogeneic kidney transplantation, organ transplant rejection.

- Adverse effects**:**

Bone marrow suppression including leukopenia (common), thrombocytopenia (less common), and/or anemia (uncommon), increased susceptibility to infections (especially varicella and herpes simplex viruses), hepatotoxicity, alopecia, GI toxicity, pancreatitis.

Mycophenolate Mofetil:

Mycophenolate mofetil (CELLCEPT) is the 2-morpholinoethyl ester of mycophenolic acid (MPA).

- Mechanism of Action:

Mycophenolate mofetil is a prodrug that is rapidly hydrolyzed to the active drug, mycophenolic acid (MPA), a selective, noncompetitive and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH), an important enzyme in the de novo pathway of guanine nucleotide synthesis. B and T lymphocytes are highly dependent on this pathway for cell proliferation while other cell types can use salvage pathways; MPA therefore selectively inhibits lymphocyte proliferation and functions including antibody formation, cellular adhesion, and migration.

- Pharmacokinetics**:** Mycophenolate mofetil undergoes rapid and complete metabolism to MPA after oral or intravenous administration. MPA, in turn is metabolized to the inactive phenolic glucuronide MPAG. Most (87%) is excreted in the urine as MPA.

- Therapeutic Uses:

Prophylaxis of transplant rejection, renal transplantation

- Adverse effects**:**

Leukopenia, diarrhoea, and vomiting, sepsis associated with cytomegalovirus, in combination with mycophenolate mofetil has been associated with devastating viral infections including polyoma nephritis [4,18,28,29].

b) Alkylating Agents

Cyclophosphamide:

Cyclophosphamide is a unique immunosuppressant as it suppresses B-lymphocyte proliferation but can enhance T-cell responses.

- Mechanism of Action:

Alkylating agents introduce alkyl groups by forming covalent bonds with nucleophilic moieties such as phosphate, sulfhydryl, hydroxyl, carboxyl, amino and imidazole groups present in DNA or RNA. By cross linking in between the strands of DNA they prevent the cell division and protein synthesis. These drugs are most destructive to rapidly proliferating tissues and appear to cause cell death when they tend to divide. The cytotoxicity of these drugs correlates with the degree of DNA alkylation.

- Therapeutic Uses:

Autoimmune disorders (including systemic lupus erythematosus), in patients with acquired factor XIII antibodies and bleeding syndromes, autoimmune hemolytic anemia, antibody-induced pure red cell aplasia, and Wegener's granulomatosis.

- Adverse effects**:** Pancytopenia and hemorrhagic cystitis, graft-versus-host disease syndrome, nausea, vomiting, cardiac toxicity and electrolyte disturbances [15,25].

IV. Cytokine Inhibitors (Anticytokine-Antibodies)-

TNF-α and IL-1 are proinflammatory cytokines implicated in pathogenesis of rheumatoid arthritis and Crohn's disease. Il-2 binds to activated T- -lymphocytes and promotes their proliferation.

TNF-α Inhibitors

Activated cytotoxic TH1 cells, macrophages and cells secrete TNF-α that to TNF receptors ($TNFR_1$ or $TNFR_2$) present on fibroblasts, neutrophils and vascular endothelial cells. Besides these, there are soluble form of TNF-α receptor present in serum and synovial fluid. Activation of TNF-α result in the release of cytokines IL-1, IL-6 and adhesion molecules that promote leukocyte activation and trafficking (migration).

Etanercept:

Is genetically engineered fusion protein composed of two soluble TNF_p75 receptors moieties linked to Fc portion of human IgG_1. The drug serves as an exogenously administered soluble TNF-α receptor and provides artificial binding sites to TNF-α. This prevents TNF-α from binding to membrane bound $TNFR_1$ and $TNFR_2$. The drug is used primarily to treat rheumatoid arthritis, and psoriatic arthritis [4,20,22].

Infliximab:

Is a Chimeric monoclonal antibody obtained by exposing the mice to human TNF- α. The antibody so produced is then fused to constant region IgG_1 to decrease the antigenicity of the drug. The drug cross links with membrane bound TNF—α receptors on cell surface to inhibit T-cell and macrophage function and to prevent the release of other proinflammatory cytokines (IL-1, IL-6 and 8 along with collagenase and metalloproteinases). Though it also has a longer half life, it does not bind TNF-β. It currently used in Cronh's disease and rheumatoid arthritis [4].

Adalimumab:

Is a human recombinant monoclonal antibody to TNF-α. It is less antigenic than Infliximab as it does not contain any foreign component. Its serum half life is 2 weeks. Patients of rheumatoid arthritis may therefore administer single dose of 40 mg/0.8 ml subcutaneously every 14 days [15].

V. Antibodies Against Specific Immune Cell Molecules-

a) Polyclonal Antibodies

Antithymocyte Globulin (ATG):

Antithymocyte globulin is a purified gamma globulin from the serum of rabbits immunized with human thymocytes.

- Mechanism of Action:

Antithymocyte globulin contains cytotoxic antibodies that bind to CD2, CD3, CD4, CD8, CD11a, CD18, CD25, CD44, CD45, and HLA class I and II molecules on the surface of human T lymphocytes. The

antibodies deplete circulating lymphocytes by direct cytotoxicity (both complement and cell-mediated) and block lymphocyte function by binding to cell surface molecules involved in the regulation of cell function.

- Therapeutic Uses:

Acute renal transplant rejection, recovery from ischemic reperfusion injury.

- Adverse effects:

Fever and chills, hypotension, Serum sickness, glomerulonephritis, leukopenia and thrombocytopenia, increased risk of infection and malignancy especially when multiple immunosuppressive agents are combined [4,15,18,20].

a) Monoclonal Antibodies

Muromunab (Anti CD-3 Antibodies, OKT-3):

Antibodies directed at the chain of CD3, a trimeric molecule adjacent to the T-cell receptor on the surface of human T lymphocytes, have been used with considerable efficacy since the early 1980s in human transplantation.

- Mechanism of Action:

Muromonab-CD3 binds to the chain of CD3, a monomorphic component of the T-cell receptor complex involved in antigen recognition, cell signaling and proliferation. Antibody treatment induces rapid internalization of the T-cell receptor, thereby preventing subsequent antigen recognition. Administration of the antibody is followed rapidly by depletion and extravasation of a majority of T cells from the bloodstream and peripheral lymphoid organs such as lymph nodes and spleen.

This absence of detectable T cells from the usual lymphoid regions is secondary both to cell death following complement activation and activation-induced cell death and to margination of T cells onto vascular endothelial walls and redistribution of T cells to nonlymphoid organs such as the lungs. Muromonab-CD3 also reduces function of the remaining T cells, as defined by lack of IL-2 production and great reduction in the production of multiple cytokines, perhaps with the exception of IL-4 and IL-10.

- Therapeutic Uses:

Acute organ transplant rejection.

- Adverse effects:

Cytokine release syndrome, high fever, chills/rigor, headache, tremor, nausea/vomiting, diarrhea, abdominal pain, malaise, myalgias, arthralgias, and generalized weakness. Less common complaints include skin reactions and cardiorespiratory and CNS disorders, including aseptic meningitis. Potentially fatal severe pulmonary edema, acute respiratory distress syndrome, cardiovascular collapse, cardiac arrest [4,15,18,21].

VI. Inhibitors of Immune Cell Adhesion:

Efalizumab

Efalizumab (LFA-1 Inhibitor) is a humanized IgG_1 mAb targeting the CD11a chain of LFA-1 (lymphocyte function associated antigen).

- Mechanism of action:

Efalizumab binds to LFA-1 and prevents the LFA-1-ICAM (intercellular adhesion molecule) interaction to block T-cell adhesion, trafficking, and activation.

- Pharmacokinetics:

Pharmacokinetic and pharmacodynamic studies showed that efalizumab produced saturation and 80% modulation of CD11a within 24 hours of therapy.

- Therapeutic Uses:

Survival of murine skin and heart allografts and monkey heart allografts, psoriasis, renal transplantation [4].

VIII. Miscellaneous-

Rho (D) Immune Globulin:

Rh_o (D) immune globulin is a concentrated (15%) solution of human IgG containing a higher titer of antibodies against the Rh_o (D) antigen of the red cell.

- Therapeutic uses:

Hemolytic disease of the newborn [15,28].

2. Immunostimulants

In contrast to immunosuppressive agents that inhibit the immune response in transplant rejection and autoimmunity, a few immunostimulatory drugs have been developed with applicability to infection, immunodeficiency, and cancer. These works on cellular as well as humoral immune system or both [15].

I. Bacillus Calmette-Guerin (BCG):

Live bacillus Calmette-Guerin (BCG; TICE BCG, THERACYS) is an attenuated, live culture of the bacillus of Calmette and Guerin strain of *Mycobacterium bovis.*

- Mechanism of action:

Induction of a granulomatous reaction at the site of administration.

- Therapeutic uses:

Treatment and prophylaxis of carcinoma of the urinary bladder, prophylaxis of primary and recurrent stage Ta and/or T1 papillary tumors after transurethral resection.

- Adverse effects:

Hypersensitivity, shock, chills, fever, malaise, and immune complex disease [4, 15].

II. Levamisole:

Levamisole (ERGAMISOL) was synthesized originally as an anthelmintic but appears to restore depressed immune function of B lymphocytes, T lymphocytes, monocytes and macrophages [16].

- Therapeutic uses:

Adjuvant therapy with 5-fluorouracil after surgical resection in patients with Duke's stage C colon cancer, agranulocytosis.

- Adverse effects:

Flu-like symptoms, allergic manifestation, nausea and muscle pain [4].

III. Thalidomide:

- Mechanism of action:

Thalidomide has been reported to decrease circulating TNF-α in patients with erythema nodosum leprosum, but to increase it in patients who are HIV-seropositive. Alternatively, it has been suggested that the drug affects angiogenesis.

- Therapeutic uses:

Severe, refractory rheumatoid arthritis [4,15,18].

- Adverse effects: Teratogenicity

IV. Recombinant Cytokines [4, 18, 30]

Table 2: Recombinant cytokines

Sr. No.	Types	Examples	Mode of action	Therapeutic uses	Adverse effects
1	Interferons	Alpha, beta, gamma	Induction of certain enzymes, inhibition of cell proliferation, and enhancement of immune activities, including increased phagocytosis by macrophages and augmentation of specific cytotoxicity by T lymphocytes.	Hairy cell leukemia, malignant melanoma, follicular lymphoma, AIDS-related Kaposi's sarcoma, chronic hepatitis B and condylomata acuminata.	Hypotension, arrhythmias, and rarely cardiomyopathy and myocardial infarction, GI distress, anorexia, weight loss, myalgia and depression.
2	Interleukins	Aldesleukin, des-alanyl-1, serine-125 human IL-2	Cellular immunity is profoundly activated with lymphocytosis, eosinophilia, thrombocytopenia, and release of multiple cytokines (e.g., TNF, IL-1 and interferon-g).	Metastatic renal cell carcinoma and melanoma.	Capillary leak syndrome, Hypotension, reduced organ perfusion, and death.
3	Colony-stimulating factors	Filgrastim (r-metHuG-CSF),	Increases the number and differentiation of myeloid progenitors.	Leucopenia, ganciclovir-induced neutropenia.	Myocardial infarction, anorexia,

V. Isoprinosine:

Isoprinosine (Inosiplex) is a complex of the pacetamidobenzoate salt of N,N-dimethylamino-2- propanol: inosine in a 3:1 molar ratio.

- Mechanism of action:

Isoprinosine has been shown to augment production of cytokines such as IL-1, IL-2 and IFN-γ. It increases proliferation of lymphocytes in response to mitogenic or antigenic stimuli, increases active T-cell rosettes and induces T-cell surface markers on prothymocytes.

- Therapeutic uses:

Herpes simplex infections, subacute sclerosing panencephalitis, acute viral encephalitis caused by herpes simplex, Epstein-Barr and measles viruses,

- Adverse effects:

Minor CNS depressant, transient nausea and rise of uric acid in serum and urine [30].

VI. Immunocynin:

It is a stable form of haemocynin, a non-haeme, oxygen carrying, copper-containing protein found in arthropods and molluses.

- Therapeutic uses:

Urinary bladder cancer.

- Adverse effects:

Rare-mild fever[30].

CONCLUSION

From this review it was concluded that immunology is probably one of the most rapidly developing areas of medical biotechnology research and has great promises with regard to the prevention and treatment of a wide range of disorders, the inflammatory diseases of skin, gut, respiratory tract, joints and central organs. Immunomodulators are going to be a central part of 21st medicine. Helping the body help itself by optimizing the immune system is of central importance in a society so stressed, unhealthily nourished and exposed to toxins that most of us are likely to have compromised immune systems. Immunomodulation, however, is a normalizing process, which correct weak immune systems and temper immune systems that are overactive, but they do not boost the immune system. Immunomodulators are becoming a viable adjunct to established modalities offering a novel approach for the treatment of infectious disease in the coming decades of 21st century.

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