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Immunomodulator: Conventional and Recent Trends

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ABSTRACT

Immunomodulators are natural or synthetic substances that help in regulation or normalize or modify the immunity of an individual to favor a particular immunological response. Immunomodulator corrects immune systems that are out of balance. Natural immunomodulators are less potent than prescription immunomodulators. Synthetic immunomodulators medications, work by suppressing immune system and decreasing inflammation in the digestive tract in people with inflammatory bowel disease, ulcerative colitis etc. The benefits of immunomodulators are from their ability to stimulate natural and adaptive defense mechanisms, such as cytokines, which enables the body to help itself. Two types of immunomodulators: Immunosuppressants; agents which suppress immune system and used for the control of pathological immune response in autoimmune disease and Immunostimulants; agents which used to enhance body's resistance against infections. A large number of disorders such as immunodeficiency state, autoimmune disease, cancer and viral infection can be treated with immunostimulants drugs.

Keywords: Immunostimulants, Immunosuppressants, Levamisole, Cyclosporine.

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INTRODUCTION

An Immunomodulator is any substance that helps to regulate the immune system. The interest in immunomodulators is increasing due to an expanding knowledge of immune function and a greater awareness that many human diseases are medicated or are associated with immune abnormalities of pathological significance**.** Immunomodulators are under development for the treatment of these diseases in which an abnormal immune response plays an important pathological role including cancer [1-2], autoimmune diseases and natural or acquired immune deficiency syndromes.

Immunomodulators is employed in immunosuppressive drug therapy for organ transplants and moreover also employed in biologic induction therapy. In many transplant centers, induction therapy with biologic agents is used to delay the use of the nephrotoxic calcineurin inhibitors or to intensify the initial immunosuppressive therapy inpatients at high risk of rejection.

Immunomodulator are also useful in the maintenance immunotherapy. Therapy typically involves a calcineurin inhibitor (cyclosporine or tacrolimus) [3], glucocorticoids, and mycophenolate mofetil [4] (a purine metabolism inhibitor), each directed at a discrete site in T-cell activation. Alternatively, sirolimus [5] can be used to limit exposure to the nephrotoxic calcineurin inhibitors. Glucocorticoids, azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, and various monoclonal and polyclonal antibodies [6] are all approved for use in transplantation.

Azathioprine and mercaptopurine work to keep people who have Crohn's disease [7]. Monoclonal and polyclonal antibodies directed at reactive T cells are important adjunct therapies and provide a unique opportunity to target specifically immune-reactive cells. Glucocorticoids limit allergic reactions that occur with other immunosuppressive agents and are used in transplant recipients. Tacrolimus is indicated for the prophylaxis of solid-organ allograft rejection. Sirolimus is indicated for prophylaxis of organ transplant rejection in combination with a calcineurin inhibitor and glucocorticoids.

Immune system

An immune system is a collection of mechanisms within an organism that protects against infection by identifying and killing pathogens and tumor cells. It detects a wide variety of pathogens, such as viruses and parasitic worms and distinguishes them from the organism's normal cells and tissues.

The immune system has a series of dual natures, the most important of which is self/non-self

recognition. The others are: general/specific, natural/adaptive = innate/acquired, cell-mediated/humeral, active/passive [8].

Table: 1 Difference between Innate & Adaptive immune system [9]

Types of the immune system	
Innate immune system	**Adaptive immune system**
Response is non-specific	Pathogen and antigen specific response
Exposure leads to immediate maximal response	Lag time between exposure and maximal response
Cell-mediated and humeral components	Cell-mediated and humeral components
No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in jawed vertebrates

Cell-mediated immunity

Macrophages engulf antigens, process them internally, and then display parts of them on their surface together with some of their own proteins. This sensitizes the T cells to recognize these antigens. CD stands for cluster of differentiation and there are more than one hundred and sixty clusters. CD8+ is read "CD8 positive." Every T and B cell has about 10^5 = 100,000molecules on its surface. B cells are coated with CD21, CD35, CD40, and CD45 in addition to other non-CD molecules.

Cytotoxic or killer T cells (CD8+) do their work by releasing lymphotoxins, which cause cell lysis. Helper T cells (CD4+) serve as managers, directing the immune response. Suppressor T cells inhibit the production of cytotoxic T cells. Memory T cells are programmed to recognize and respond to a pathogen once it has invaded and been repelled.

Humoral immunity

An immunocompetent but as yet immature B-lymphocyte is stimulated to maturity when an antigen binds to its surface receptors. This sensitizes the B cell and it undergoes clonal selection. These cells, after an initial lag, produce highly specific antibodies.

Antibodies, also called immunoglobulins or Igs constitute the gamma globulin part of the blood proteins. The antibodies inactivate antigens by, (a) complement, (b) neutralization, (c) agglutination, (d) precipitation and other more methods.

Lymphocytes

B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow. Both B cells and T cells carry receptor molecules that recognize specific targets. T cells recognize a “non-self” target, such as a pathogen, only after antigens have been processed and presented in combination with a “self” receptor called a major

histocompatibility complex (MHC) molecule. There are two major subtypes of T cells: the killer T cell and the helper T cell. Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells only recognize antigens coupled to Class II MHC molecules. These two mechanisms of antigen presentation reflect the different roles of the two types of T cell. T cells are involved in cell-mediated immune response.

TYPES OF IMMUNOMODULATORS

Depending upon the stimulant and suppressant effects exerted by these drugs on immune system they are categorized as:

- Immunosuppressants
- Immunoenhancers or Immunostimulants

Immunosuppressants

These are drugs which inhibit cellular/humoral or both immune response and have their major use in organ transplantation and autoimmune disease.

The major classes of immunosuppressive drugs are:

(1) Glucocorticoids

(2)Antiproliferative/antimetabolic agent

(3) Calcineurin inhibitors

(4) Biologicals (antibodies).

Glucocorticoids

In pharmacologic doses, glucocorticoids such as prednisone and prednisolone are used alone or in combination with other agents to suppress various allergic, inflammatory, and autoimmune disorders. They are also administered as post transplantory immunosuppressant to prevent the acute transplant rejection and graft-versus-host disease.

Glucocorticoids act by suppressing 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 cause B cells to express smaller amounts of IL-2 and of IL-2 receptors [10]. This diminishes both B cell clone expansion and antibody synthesis.

Anti-inflammatory effects of glucocorticoids influence all types of inflammatory events. They induce the lipocortin-1synthesis, which then binds to cell membranes preventing the phospholipase A2 from coming into contact with its substrate arachidonic acid. This leads to diminished eicosanoid production. The cyclooxygenase expression is also suppressed, potentiating the effect. Glucocorticoids also stimulate the lipocortin-1 escaping to the

extracellular space, where it binds to the leukocyte membrane receptors and inhibits various inflammatory events: epithelial adhesion, emigration, chemotaxis, phagocytosis, respiratory burst and the release of various inflammatory mediators from neutrophils, macrophages and mastocytes.

Antiproliferative/antimetabolic agents

Sirolimus:

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

Sirolimus act by inhibiting T-lymphocyte activation and proliferation downstream of the IL-2 and other T-cell growth factor receptors. Therapeutic action of sirolimus requires formation of a complex with an immunophilin, in this case FKBP-12(FK506-binding protein).The sirolimus–FKBP-12 complex inhibits a protein kinase that is a key enzyme in cell-cycle progression, designated mTOR (mammalian target of rapamycin). Inhibitions of mTOR blocks cell-cycle progression at the G1 → S phase transition.

After oral administration, sirolimus is absorbed rapidly and reaches a peak blood concentration within ~1 hour after a single dose in healthy subjects and within~2 hours after multiple oral doses in renal transplant patients. A high-fat meal decreases peak blood concentration by 34%; sirolimus therefore should be taken consistently either with or without food. About 40% of sirolimus in plasma is protein bound, especially to albumin. Sirolimus is extensively metabolized byCYP3A4 and is transported by P-glycoprotein.

Sirolimus is therapeutically indicated for prophylaxis of organ transplant rejection in combination with a calcineurin inhibitor and glucocorticoids. It is recommended that the maintenance dose be reduced by approximately one-third in patients with hepatic impairment. Sirolimus also has been incorporated into stents to inhibit local cell proliferation and blood vessel occlusion [11].

Toxicity of sirolimus in renal transplant patients is associated with a dose-dependent increase in serum cholesterol and triglycerides. Sirolimus prolong delayed graft function in deceased donor kidney transplants, presumably because of its antiproliferative action. Lymphocele, a surgical complication associated with renal transplantation, is increased in a dose-dependent fashion by sirolimus, requiring close postoperative follow-up. Other adverse effects include anemia, leukopenia, thrombocytopenia, hypo- or hyperkalemia, fever, and GI effects.

Everolimus

Everolimus (40-*0*-[2-hydroxy] ethyl-rapamycin) is closely related chemically and clinically to

sirolimus but has distinct pharmacokinetics. The main difference is a shorter $t_{1/2}$. Dosage on mg/kg basis is similar to sirolimus. As with sirolimus, the combination of a calcineurin inhibitor and an mTOR inhibitor [12] produces worse renal function at 1 year than calcineurin inhibitor therapy alone, suggesting a drug interaction between the mTOR inhibitors and the calcineurin inhibitors to enhance toxicity and to reduce rejection. The toxicity of everolimus and the drug interactions seem to be the same as with sirolimus.

Azathioprine

Azathioprine (IMURAN) is a purine antimetabolite. It is an imidazole derivative of 6-mercaptopurine. Azathioprine act by 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 [13]. 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 avariety of lymphocyte functions. Azathioprine appears to be a more potent immunosuppressive agent than 6-mercaptopurine.

Azathioprine is well absorbed orally and reaches maximum blood levels within 1–2 hours after administration. The $t_{1/2}$ of azathioprine is ~10 minutes, while that of its metabolite 6-mercaptopurine is about an hour. Azathioprine and mercaptopurine are moderately bound to plasma proteins and are partially dialyzable. Both are rapidly removed from the blood by oxidation or methylation in the liver and/or erythrocytes.

Azathioprine is indicated as an adjunct for prevention of organ transplant rejection and in severe rheumatoid arthritis. Lower initial doses (1 mg/kg/day) are used for rheumatoid arthritis.

Toxicity of azathioprine is bone marrow suppression, including leukopenia, thrombocytopenia. Other important adverse effects include increased susceptibility to infections, hepatotoxicity, alopecia, GI toxicity, pancreatitis, and increased risk of neoplasia.

Azathioprine interacts with Xanthine oxidase, a key enzyme in the catabolism of azathioprine metabolites, which is blocked by allopurinol. If azathioprine and allopurinol are used concurrently, the azathioprine dose must be decreased to 25–33% of the usual dose. Adverse effects resulting from co administration of azathioprine with other myelosuppressiveagents [14] or angiotensin-converting enzyme inhibitors include leukopenia, thrombocytopenia, and anemia.

Mycophenolate mofetil

Mycophenolate mofetil (CELLCEPT) is the 2-morpholinoethylester of mycophenolic acid (MPA). Mycophenolate mofetil act by hydrolyzing to MPA, a selective, noncompetitive, and reversible inhibitor of inosine monophosphate dehydrogenase (IMPDH) [15], 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.

Mycophenolate mofetil is completely metabolized to MPA after oral or intravenous administration. MPA, in turn, is metabolized to the inactive glucuronide MPAG. The parent drug is cleared from the blood within a few minutes. The $t_{1/2}$ of MPA is ~16 hours. Most (87%) is excreted in the urine as MPAG. Plasma concentrations of MPA and MPAG are increased in patients with renal insufficiency. In early renal transplant patients, plasma concentrations of MPA after a single dose of mycophenolate mofetil are approximately half of those found in healthy volunteers.

Mycophenolate mofetil is indicated for prophylaxis of transplant rejection, and it typically is used in combination with glucocorticoids and a calcineurin inhibitor. A higher dose, 1.5 g twice daily (3g/day), is recommended renal transplant patients and all cardiac transplant patients.

The principal toxicities of mycophenolate mofetil are leukopenia, diarrhea, and vomiting. Tacrolimus in combination with mycophenolate mofetil has been associated with devastating viral infections including polyoma nephritis.

Tacrolimus interact by delaying elimination of mycophenolate mofetil by impairing the conversion of MPA to MPAG. This may enhance GI toxicity. Mycophenolate mofetil should not be administered with cholestyramine or other drugs that affect enterohepatic circulation. Acyclovir and ganciclovir may compete with MPAG for tubular secretion.

Cyclophosphamide

This cytotoxic drug [16] has more marked effect on B cells and humoral immunity compared to that on T cells and cell-mediated immunity. It has been particularly utilized in bone marrow transplantation in which a short course with high dose is generally given. In other organ transplants it is employed only as a reserve drug. In rheumatoid arthritis, it is rarely used, only when systemic manifestations are marked. Low doses are occasionally employed for maintenance therapy in pemphigus, systemic lupus erythematosus and idiopathic thrombocytopenic purpura.[17]

Methotrexate

This folateantagonist is a potent immunosuppressant which markedly depresses cytokine production and cellular immunity, and has anti inflammatory property. It has been used as a first line drug in many autoimmune diseases like rapidly progressing rheumatoid arthritis, severe

psoriasis, pemphigus, myasthenia gravis, and chronic hepatitis. Low dose Mtx maintenance therapy is relatively well tolerated.

Chlorambucil

Chlorambucil (LEUKERAN) is used in treating childhood nephrotic syndrome [18] and a variety of malignancies. It has relatively weak immunosuppressant action which is sometimes utilized in autoimmune diseases and transplant maintenance regimens.

FTY720

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) [19] 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.

Calcineurin inhibitors

The most effective immunosuppressive drugs in routine use are the calcineurin inhibitors, cyclosporine and tacrolimus, which target intracellular signaling pathways induced as a consequence of T-cell–receptor activation. Although they are structurally unrelated and bind to distinct molecular targets, they inhibit normal T-cell signal transduction essentially by the same mechanism.

Cyclosporine

Cyclosporine (Sandimmune) is a potent inhibitor of antibody-and cell-mediated immune responses and is the immunosuppressant of choice for the prevention of transplant rejection. It also has application in the treatment sof autoimmune diseases. Cyclosporine is a highly stable 11–amino acid cyclic polypeptide. It can be administered intravenously, orally, or by injection.

Cyclosporine act by binding to the cytosolic protein cytophilin-C [20]. This drug–protein complex inhibits calcineurin phosphatase activity, which leads to a decreased synthesis and release of several cytokines, including interleukins IL-2, IL-3, IL-4, interferon, and tumor necrosis factor.

Cyclosporine exhibits a high degree of specificity in its actions on T cells without significantly impairing Bcell activity. It can inhibit the T cell–dependent limb of antibody production by lymphocytes by preventing the differentiation of B cells into antibody-secreting plasma cells. Because T cells appear to require IL-2 stimulation for their continuous growth, cyclosporine impairs the proliferative response of T cells to antigens. After oral administration, cyclosporine is absorbed slowly and incompletely. Peak plasma concentrations are reached in3 to 4 hours, and the plasma half-life is 10-27 hours.

The drug is extensively metabolized by hepatic mixed function oxidase enzymes and is excreted

principally via the bile. Metabolism results in inactivation of the immunosuppressive activity.

Cyclosporine has a beneficial effect on the course of rheumatoid arthritis, uveitis, insulin dependent diabetes, systemic lupus erythematosus, and psoriatic arthropathies in some patients. Toxicity is more of a problem in these conditions than during use in transplantation, since higher doses of cyclosporineare often required to suppress autoimmune disorders.

Toxicity of Cyclosporine is nephrotoxicity, which can occur in up to 75% of patients, ranges from severe tubular necrosis to chronic interstitial nephropathy. Vasoconstriction appears to be an important aspect of cyclosporine-induced nephrotoxicity. Hypertension occurs in25% of the and more frequently in patients' with some degree of renal dysfunction; the concomitant use of antihypertensive drugs may prove useful. Hyperglycemia, hyperlipidemia, transient liver dysfunction, and unwanted hair growth are also observed.

Tacrolimus

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

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, Ca2+, calmodulin, and calcineurin then forms, and calcineurin phosphatase activity is inhibited. As described for cyclosporine and, the inhibition of phosphatase activity prevents dephosphorylation and nuclear translocation of NFAT (nuclear factor of activated T cells) [21] and inhibits T-cell activation. Thus, although the intracellular receptors differ, cyclosporine and tacrolimus target the same pathway for immunosuppression.

Tacrolimus is orally administrated and also in sterile solution for injection (5 mg/ml). Immunosuppressive activity resides primarily in the parent drug. Whole blood, rather than plasma, is the most appropriate sampling compartment to describe tacrolimus pharmacokinetics. Target concentrations in many centers are 200–400 ng/ml in the early preoperative period and 100–200 ng/ml 3 months after transplantation.

GI absorption is incomplete and variable. Food decreases the rate and extent of absorption. Plasma protein binding of tacrolimus is 75–99%, involving primarily albumin. Tacrolimus is extensively metabolized in the liver by CYP3A, with a $t_{1/2}$ of ~12 hours; at least some of the metabolites are active.

Tacrolimus is indicated for the prophylaxis of solid-organ allograft rejection in a manner akin to cyclosporine and as rescue therapy in patients with rejection despite "therapeutic" levels of

cyclosporine. Dosages are intended to achieve blood trough levels of 5–15-ng/ml.

Nephrotoxicity, neurotoxicity, GI complaints, hypertension, hyperkalemia, hyperglycemia, and diabetes are all associated with tacrolimus use. Tacrolimus has a negative effect on pancreatic Bcells, and glucose intolerance and diabetes mellitus are well-recognized complications of tacrolimus-based immunosuppression. As with other immunosuppressive agents, there is an increased risk of secondary tumors and opportunistic infections.

Because of its potential for nephrotoxicity, tacrolimus blood levels and renal function should be monitored closely, especially when tacrolimus is used with other potentially nephrotoxic drugs. Co administration with cyclosporine results in additive or synergistic nephrotoxicity; therefore, a delay of at least 24 hours is required when switching a patient from cyclosporine to tacrolimus.

Biologicals (antibodies)

Both polyclonal and monoclonal antibodies against lymphocyte cell-surface antigens are widely used for prevention and treatment of organ transplant rejection. Monoclonal reagents have overcome the problems of variability in efficacy and toxicity seen with the polyclonal products, but they are more limited in their target specificity. First-generation murine monoclonal antibodies generally have been replaced by newer chimeric or humanized monoclonal antibodies that lack antigenicity, have prolonged half-lives, and can be mutagenized to alter their affinity to receptors.

Antithymocyte globulin

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

Antithymocyte globulin act by binding 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 and block lymphocyte function by binding to cell surface molecules involved in the regulation of cell function.

Antithymocyte globulin is used for induction immunosuppression, although the only approved indication is in the treatment of acute renal transplant rejection in combination with other immunosuppressive agents. Antilymphocyte-depleting agents (THYMOGLOBULIN, ATGAM) are thought to improve graft survival. A course of antithymocyte-globulin treatment often is given to renal transplant patients with delayed graft function to avoid early treatment with the nephrotoxic calcineurin inhibitors [22].

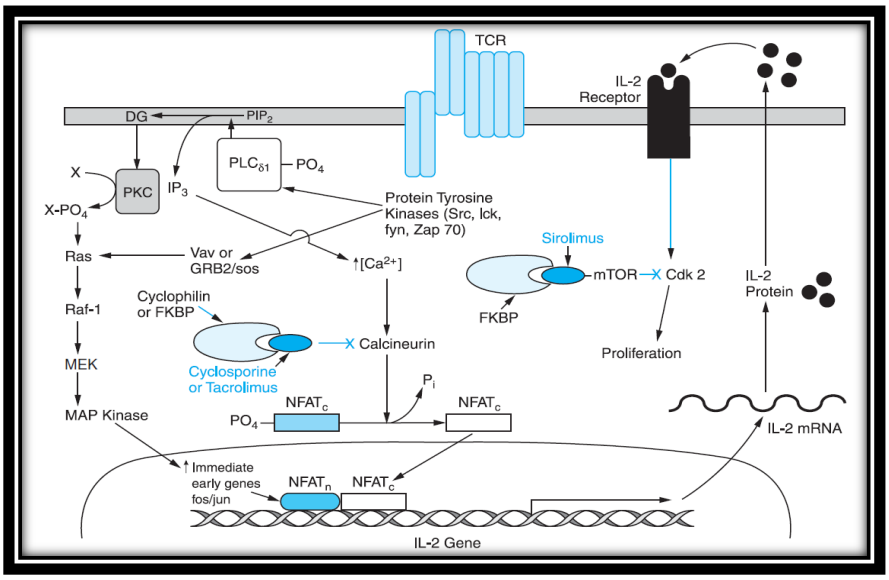

Figure: Mechanisms of action of cyclosporine, tacrolimus, and sirolimus on T cells

Monoclonal Antibodies

Anti-CD3 Monoclonal Antibodies

Antibodies directed at the *e* 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 in human transplantation. The original mouse IgG2antihuman CD3 monoclonal antibody, muromonab-CD3 (OKT3, ORTHOCLONE OKT3), still is used to reverse glucocorticoid-resistant rejection episodes.

Muromonab-CD3 act by binding to the e chain of CD3, a 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 following, 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.

Muromonab-CD3 is indicated for treatment of acute organ transplant rejection. The recommended dose is 5 mg/day in a single intravenous bolus (<1 minute) for 10–14 days. Antibody levels increase over the first 3 days. Circulating T cells disappear from the blood within minutes of administration and return within ~1 week after cessation of therapy. Repeated use of muromonab-CD3 results in the immunization of the patient against the mouse determinants of the antibody, which can neutralize and prevent its immunosuppressive efficacy.

Thus, repeated treatment with the muromonab-CD3 or other mouse monoclonal antibodies generally is contraindicated.

The major side effect of anti-CD3 therapy is the "cytokine release syndrome," [23] which typically begins 30 minutes after infusion of the antibody and may persist for hours. Antibody binding to the T-cell receptor complex combined with Fc receptor (FcR)–mediated cross-linking is the basis for the initial activating properties of this agent. The syndrome is attributed to increased serum levels of cytokines (including TNF-*a*, IL-2, IL-6, and interferon-*g*), which are released by activated T cells and/or monocytes. The symptoms usually are worst with the first dose; frequency and severity decrease with subsequent doses. Common clinical manifestations include high fever, chills/rigor, headache, tremor, nausea/vomiting, diarrhea, abdominal pain, malaise, myalgias, arthralgias, and generalized weakness. Less common complaints include skin reactions and cardio respiratory and CNS disorders, including aseptic meningitis. Potentially fatal pulmonary edema, acute respiratory distress syndrome, cardiovascular collapse, and arrhythmias have occurred [24].

Anti-IL-2 Receptor (Anti-CD25) Antibodies

Daclizumab (ZENAPAX), a humanized murine complementarily-determining region (CDR)/human IgG1 chimeric monoclonal antibody, and basiliximab (SIMULECT) [25], a murine-human chimeric monoclonal antibody, are produced by recombinant-DNA technology. Daclizumab consists of human (90%) constant domains of IgG1 and variable framework regions of the Eu myeloma antibody and murine (10%) of CDR the anti-Tac antibody.

The exact mechanism of action of the anti-CD25 mAbs is not completely understood but likely results from the binding of the anti-CD25 mAbs to the IL-2 receptor on the surface of activated, but not resting, T cells. Significant depletion of T cells does not appear to play a major role in the mechanism of action of these mAbs. Therapy with the anti-IL-2R mAbs is thought to result in a relative decrease of the expression of a chain, either from depletion of coated lymphocytes or modulation of a chain secondary to decreased expression or increased shedding.

Daclizumab and basiliximab are used for prophylaxis of acute organ rejection in adult patients. In Phase III trials, daclizumab was administered in 1 mg/kg given intravenously over 15 minutes in 50–100 ml of normal saline starting immediately preoperatively and subsequently at biweekly intervals. The $t_{1/2}$ of daclizumab was 20 days, resulting in saturation of the IL-2R*a* on circulating lymphocytes for up to 120 days after transplantation. Daclizumab has been used with maintenance immunosuppression regimens (cyclosporine, azathioprine, and glucocorticoids; cyclosporine and glucocorticoids) and with maintenance triple-therapy regimen—either with

cyclosporine or tacrolimus, glucocorticoids, and mycophenolate mofetil (MMF) substituting for azathioprine. Basiliximab administered in a fixed dose of 20 mg preoperatively and on days0 and 4 after transplantation, resulted in a concentration sufficient to saturate IL-2R on circulating lymphocytes for 25–35 days after transplantation. The $t_{1/2}$ of basiliximab was 7 days. Basiliximab has been used with a maintenance regimen consisting of cyclosporine and prednisone [26].

Campath-1H

Campath-1H (ALEMTUZUMAB) [27] is a humanized mAb that is approved for use in chronic lymphocytic leukemia. The antibody targets CD52, a glycoprotein expressed on lymphocytes, monocytes, macrophages, and natural killer cells; thus, the drug causes extensive lympholysis by inducing apoptosis of targeted cells. It has achieved some use in renal transplantation because it produces prolonged T- and B-cell depletion and allows drug minimization.

Anti-TNF Reagents

Infliximab

Infliximab (REMICADE) [28] is a chimeric anti–TNF-*a* monoclonal antibody containing a human constant region and a murine variable region. It binds with high affinity to TNF-*a* and prevents the cytokine from binding to its receptors.

TNF-*a* implicated in the pathogenesis of a number of autoimmune diseases, including rheumatoid arthritis and Crohn's disease. Infliximab plus methotrexate improves the signs and symptoms of rheumatoid arthritis more than methotrexate alone. Patients with active Crohn's disease, who had not responded to other therapies, including those with fistulae, also improved when treated with infliximab. Infliximab is approved for treating the symptoms of rheumatoid arthritis and is used in combination with methotrexate in patients who do not respond to methotrexate alone. Infliximab also is approved for treatment of symptoms of moderate-to-severe Crohn's disease in patients who have failed to respond to conventional therapy and in treatment to reduce the number of draining fistulae in Crohn's disease patients.

About one of six patients receiving infliximab experience an infusion reaction, characterized by fever, urticaria, hypotension, and dyspnea, within 1–2 hours after antibody administration. Serious infections also have occurred in infliximab-treated patients, most frequently in the upper respiratory and urinary tracts.

LFA-1 Inhibition

Efalizumab

Efalizumab (RAPTIVA) [29] is a humanized IgG1 mAb targeting the CD11a chain of LFA-1 (lymphocyte function associated antigen). Efalizumab binds to LFA-1 and prevents theLFA-1–

ICAM (intercellular adhesion molecule) interaction to block T-cell adhesion, trafficking and activation. Efalizumab is approved for use in patients with psoriasis. Efalizumab is given as weekly subcutaneous injections. The first dose is 0.7 mg/kg of body weight. Thereafter, each weekly dose is 1 mg/kg. Pharmacokinetic and pharmacodynamic studies showed that efalizumab produced saturation and 80% modulation of CD11a within 24 hours of therapy. Efalizumab appears to be an effective immunosuppressive agent, for transplant rejection, it may be best used in a lower dose and with an immunosuppressive regimen that avoids calcineurin inhibitors.

Rho (D) Immune Globulin

An Rh-negative mother can become sensitized to Rh antigen during delivery of an Rh-positive infant. This sensitization may lead to Rh hemolytic disease in future newborns. Rho (D) immune globulin (RhoGAM) is a preparation of human IgG that contains a high titer of antibodies against the Rh (D) red cell antigen. Rho (D) immune globulin functions to prevent the mother from becoming sensitized to the Rh antigen by binding to and destroying fetal red blood cells that have enter in blood. It is generally given at 28 weeks of pregnancy and within 72 hours after delivery. Rh incompatibility can be identified with routine blood tests [30].

IMMUNOENHANCERS OR IMMUNOSTIMULANTS

Immunosuppressive agents which inhibit the immune response in transplant rejection and autoimmunity, a few immunostimulatory drugs have applicability to infection, immunodeficiency, and cancer.

Levamisole

Levamisole (ERGAMISOL) was synthesized originally as an anthelmintic but appears to "restore"depressed immune function of B lymphocytes, T lymphocytes, monocytes, and macrophages. Its only clinical indication is as adjuvant therapy with 5-fluorouracil after surgical resection in patients with Dukes' stage C colon cancer. It occasionally has been associated with fatal agranulocytosis [31].

Bacillus calmette-guérin (BCG)

Live bacillus Calmette-Guérin (BCG; TICE BCG, THERACYS) is an attenuated culture of the bacillus of Calmette and Guérin strain of Mycobacterium bovis, which induces a granulomatous reaction at the site of administration. This preparation is active against tumors and is indicated for treatment and prophylaxis of carcinoma in situ of the urinary bladder and for prophylaxis of primary and recurrent stage Ta and/or T1 papillary tumors after transurethral resection. Adverse effects include hypersensitivity, shock, chills, fever, malaise, and immune complex disease [32].

Thymic factors

Thymic factors are naturally occurring substances that promote T-lymphocyte differentiation and differentiation of early stem cells into prothymocytes. Each of the available preparations (e.g., thymic humoral factor, thymosin fraction 5, and thymodulin) is mixtures of several polypeptides isolated from a calf thymus extract. By promoting the formation of T lymphocytes, thymic factors are used to enhance T-lymphocytic functions. Thymic factors have been used with some success in clinical trials in patients with severe combined immunodeficiency, DiGeorge's or Nezelof's syndrome, and viral disorders. Studies with thymodulin show promise in treating symptoms in asthmatics and patients with allergic rhinitis. The primary consideration in the use of thymic factors for immunodeficiency states is the presence of T-lymphocyte precursors [33].

Recombinant cytokines

Interferons

Although interferons (a, b, and g) initially were identified by their antiviral activity, these agents also have important immunomodulatory activities. The interferons bind to specific cell-surface receptors that initiate a series of intracellular events: 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. Recombinant interferon alfa-2b (IFN-alpha 2, INTRON A) is obtained by recombinant expression in E. coli. It is a member of a family of naturally occurring small proteins with molecular weights of 15–27.6 KDa, produced and secreted by cells in response to viral infections and other inducers. Interferon alfa-2bis indicated in the treatment of a variety of tumors, including hairy cell leukemia, malignant melanoma, follicular lymphoma, and AIDS-related Kaposi's sarcoma. It also is indicated for chronic hepatitis B infection and condylomata acuminata. It is supplied in combination with ribavirin(REBETRON) for treatment of chronic hepatitis C in patients with compensated liver function not treated previously with interferon alfa-2b or who have relapsed after interferon alfa-2b therapy. Flu-like symptoms, including fever, chills, and headache, are the most common adverse effects after interferon alfa-2b administration. Adverse effects involving the cardiovascular system (hypotension, arrhythmias, and rarely cardiomyopathy and myocardial infarction) and CNS are less frequent.

Interferon gamma-1b (ACTIMMUNE) is a recombinant polypeptide that activates phagocytes and induces their generation of oxygen metabolites that are toxic to a number of microorganisms. It is indicated to reduce the frequency and severity of serious infections associated with chronic granulomatous disease. Adverse reactions include fever, headache, rash, fatigue, GI distress, anorexia, weight loss, myalgia, and depression.

Interferon beta-1a (AVONEX, REBIF), a 166–amino acid recombinant glycoprotein, and interferonbeta-1b (BETASERON), a 165–amino acid recombinant protein, have antiviral and immunomodulatory properties. They are FDA-approved for the treatment of relapsing-remitting multiple sclerosis to reduce the frequency of clinical exacerbations. Flu-like symptoms are common adverse effects [34].

Interleukin-2

Human recombinant IL-2 (aldesleukin, PROLEUKIN; des-alanyl-1, serine-125human IL-2) differs from native IL-2 in that it is not glycosylated, has no amino terminal Ala, and has a Ser substituted for the Cys at amino acid 125. Aldesleukin has the following in vitro biologic activities of native IL-2: enhancement of lymphocyte proliferation and growth of IL-2–dependent cell lines; enhancement of lymphocyte-mediated cytotoxicity and killer cell activity; and induction of interferon-g activity. In vivo administration of aldesleukin in animals produces multiple immunologic effects in a dose-dependent manner. Cellular immunity is profoundly activated with lymphocytosis, eosinophilia, thrombocytopenia, and release of multiple cytokines. Aldesleukin is indicated for the treatment of adults with metastatic renal cell carcinoma and melanoma. Administration of aldesleukin has been associated with serious cardiovascular toxicity resulting from capillary leak syndrome, which involves loss of vascular tone [35].

OTHER IMMUNNOMODULATORS

Cimetidine

Cimetidine has immunomodulatory effects that include blocking suppressor T cells and facilitating cell-mediated immunity. The histamine-induced upregulation of IL-6 and IL-8 production, however, may be completely abrogated by a combination of pyrilamine and cimetidine. In patients with allergic rhinitis, cimetidine decreases the number of $CD4^+$ and increases the number of $CD8^+$ lymphocytes. Cimetidine and famotidine slightly reduce the O_2^- or H_2O_2 production of neutrophils in a dose dependent manner. It decreases interleukin 6 production by human keratinocytes [36].

Licopid

Licopid is a new semisynthetic drug of natural origin. As an immunomodulator Licopid can suppress autoimmune reaction. Licopid can use in combination with antibiotics and anti-viral drugs to reduce their dose without reduction in therapeutic efficacy. Licopid act by increasing general resistance against pathogens by activating phagocyte cells. These cells ingest and destroy pathogenic microorganisms and at the same time, they secrete cytokines, which affect T-and B-lymphocytes and thus support the development of specific immune response [37].

RECENTTRENDS OF IMMUNOMODULATING DRUGS

CYC682

CYC682 is an oral small molecule nucleoside analogue appears to exert its anticancer activity both by delaying cell cycle progression during S phase and inducing arrest at the G2 phase of the cell cycle [38].

HGS-ETR2

HGS-ETR2 is a human monoclonal antibody that mimics the activity of TRAIL (tumor necrosis factor-related apoptosis-inducing ligand-receptor), but with greater specicity and considerably longer serum half-life.HGS-ETR2 binds to TRAIL Receptor-2 and triggers cell death by apoptosis.

L-001079038

L-001079038 is a potent inhibitor of histone deacetylase (HDAC), an enzyme that is important in gene transcription regulation. HDAC inhibitors can induce differentiation, growth arrest, and apoptosis of transformed cells.

TRM-1

TRM-1 is a fully human monoclonal antibody that binds TRAIL-R1 with high affinity and induces cell death in sensitive cancer cell lines. It is administered as an intravenous infusion once every 28 days [39].

CONCLUSION

Immunomodulators are substances, which by altering the immune system affect therapeutic benefits. They are introduced into the body, which activates the macrophages and the granulocytes, thereby increasing the phagocytosis. Immunosuppressive drugs (glucocorticoids, calcineurin inhibitors, anti proliferative agent and antibodies) are used to depress the immune response in the organ transplant and auto-immune diseases. Immunostimulants (Levamisole and Thalidomide) are used to stimulate the immune response. Many drugs are under different stages of clinical trial. In the near future we should expect noble immunomodulating products reaching the market. It may provide long term treatment such as treatment of HIV, tumor and organ transplantation also in specific immunotherapy.

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