57 Immunomodulating Drugs

Leonard J. Sauers

DRUG LIST

Immunopharmacology is the study of the use of pharmacological agents as modulators of immune responses. The principal applications are in the use of *immunosuppressive agents* (i.e., compounds that suppress undesirable immune responses) and *immunostimulating agents* (i.e., drugs, microorganisms, or biological products that enhance or augment immune responses). Three major indications for immunotherapy are in the treatment of autoimmune diseases, primary immunodeficiency diseases, and organ transplantation.

AUTOIMMUNE DISEASES

Cells from the body's immune system can on occasion react against normal endogenous proteins and thereby effect a reaction against certain body tissues. This abnormal immune response is termed *autoimmunity.* Ordinarily, a complex network of feedback loops keeps autoimmune reactions in check. However, under certain circumstances, normal control is lost and the aberrant immune reaction will result in disease.

Myasthenia gravis is an example of an autoimmune disease in which antibodies are produced against the acetylcholine receptors in the neuromuscular junction. The abnormal immune response results in the breakdown of junctional receptors, ultimately rendering patients weak and unable to move voluntary muscles. Rheumatoid arthritis is another autoimmune disease in which antibodies are secreted against a component of an individual's own immune globulins. These antibody–immune globulin conjugates (immune complexes) form precipitates in the joints of affected individuals. Phagocytic cells are in turn attracted to these sites, where they release enzymes that destroy surrounding tissue (inflammation). *Immunosuppressive agents are often employed in debilitating cases of autoimmune disease to curb the production of autoantibodies.*

T A B L E 57.1 Some Autoimmune Disorders Treated with Immunosuppressive Therapy

Autoimmune hemolytic anemia
Myasthenia gravis
Cranial arteritis
Idiopathic thrombocytopenic purpura
Membranous glomerulonephritis
Polymyalgia rheumatica
Polymyositis
Psoriatic arthropathies
Rheumatoid arthritis
Systemic lupus erythematosus
Ulcerative colitis
Uveitis
Wegener's granulomatosis

A list of autoimmune diseases for which immunosuppressive therapy is commonly used can be found in Table 57.1.

ORGAN TRANSPLANTATION

Suppression of the immune system is a requirement during organ transplantation because of the propensity of the recipient to reject the foreign tissue by immunological mechanisms. Since transplantation is usually performed in patients with a poor prognosis for survival, the use of immunosuppressive agents has potentially great therapeutic benefit, because it provides the only real hope of continued life for many individuals. Immunosuppression, however, is frequently an adverse reaction when these drugs are used as antineoplastic drugs.

In the past, immunosuppression could be achieved only through the use of *nonspecific* cytotoxic drugs (e.g., cyclophosphamide or azathioprine), which are particularly toxic to rapidly proliferating cells, such as those of the bone marrow, gonadal tissue, and gastrointestinal tract. Consequently, serious side effects, including bone marrow depression, overwhelming infections, and sterility, limited their usefulness as immunosuppressants. The concurrent use of corticosteroids with the immunosuppressants increased the risk of additional toxicity. With the development of the immunosuppressants cyclosporine and tacrolimus it is now possible to avoid much of this toxicity. Because of their relatively low toxicity, these drugs have revolutionized the field of transplantation. It is now possible to successfully transplant tissues to patients not previously considered as candidates for transplantation.

PRIMARY IMMUNODEFICIENCY DISEASES

Primary immunodeficiency diseases (PIDs) are defects of the immune system that are due to genetic abnormalities or some failure in normal embryological development. They are usually apparent at birth or develop shortly thereafter. Approximately 70 PIDs have been described, including those specific for humoral immunity (e.g., X-linked agammaglobulinemia, immune globulin [Ig] A deficiency), cellular immunity (e.g., DiGeorge's syndrome), or both (e.g., severe combined immunodeficiency syndrome).

The treatment of a PID is based on the aspect of the immune system that is lacking. For those with deficiencies in humoral immunity, the only effective treatment available is antibody replacement (e.g., immune globulin) and medical management of infections. For those with deficiencies in cell-mediated immunity, there is no effective pharmacological treatment.

The clinical manifestations of PIDs vary with the aspect of the immune system affected. In general, because of the role of antibodies in protection against bacterial infections, individuals with deficiencies in humoral immunity are particularly prone to infections from *Streptococcus pneumoniae* and *Haemophilus influenzae.* These individuals are also prone to infections of the respiratory, gastrointestinal, and urinary tracts because of the protective role of IgA in secretions.

Individuals with defects in cellular immunity are prone to fungal, protozoal, and viral infections, such as *Candida albicans,* cytomegalovirus, and *Pneumocystis carinii,* since cell-mediated immune responses are the primary defenses against these types of infection. Because of the role of cell-mediated immunity in tumor surveillance, these individuals will also demonstrate an increased incidence of malignancy if they survive long enough.

GENERAL PRINCIPLES OF IMMUNOSUPPRESSIVE THERAPY

Before describing individual drugs, it is important to consider three principles of immunosuppressive therapy. (1) *Primary immune responses are more readily inhibited than are secondary responses.* Therefore, components of the primary phase of the immune response, such as processing, proliferation, and differentiation, will be the most sensitive to drug action. Drugs that are effective in suppressing an immune response in an unsensitized person generally will show much less effect, if any, in a sensitized individual. Once a population of memory cells has been established, immunosuppressive drugs show little effectiveness. (2) *Not all immune responses are equally affected by immunosuppressive drugs.* Cellular

and humoral immunity may be affected differentially. Additionally, the different classes of immune globulins in a humoral response may be variably affected. (3) *Beneficial effects other than immunosuppression may result from therapy with these drugs.* In particular, the antiinflammatory properties of certain of these drugs may be valuable because inflammation often accompanies the immune response. If only an inflammatory reaction is present, a true antiinflammatory drug, such as a corticosteroid, that is devoid of the many side effects of immunosuppressive agents should be used.

The focus in the next section is on immunosuppressants that have been shown to be clinically useful. Others that may hold promise in the future are mentioned briefly.

INDIVIDUAL DRUGS USED TO SUPPRESS THE IMMUNE SYSTEM

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 of autoimmune diseases.

Cyclosporine is a highly stable 11–amino acid cyclic polypeptide. The molecule is very lipophilic and essentially is not soluble in water. It can be administered intravenously, orally, or by injection.

Mechanism of Action

Cyclosporine can bind to the cytosolic protein cytophilin C. 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-α, and tumor necrosis factor.

Cyclosporine exhibits a high degree of specificity in its actions on T cells without significantly impairing B-cell 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. However, once T cells have been stimulated by antigens to synthesize IL-2, cyclosporine cannot suppress the proliferation of T cells induced by this cytokine.

Absorption, Metabolism, and Excretion

After oral administration, cyclosporine is absorbed slowly and incompletely, with great variation among individuals. Peak plasma concentrations are reached in 3 to 4 hours, and the plasma half-life is 10 to 27 hours. The drug is extensively metabolized by hepatic mixed-function oxidase enzymes and is excreted principally via the bile into the feces. Metabolism results in inactivation of the immunosuppressive activity. Agents that enhance or inhibit the mixed-function oxidase enzymes will alter the therapeutic response to cyclosporine.

Clinical Uses

Cyclosporine has been approved for use in allogeneic kidney, liver, and heart transplant patients and is under study for use in pancreas, bone marrow, single lung, and heart–lung transplant procedures. It is recommended that corticosteroids, such as prednisone, be used concomitantly, although at half or less of their usual dose. Such combined therapy leads to fewer side effects, a decreased incidence of infectious complications, efficacy of lower doses of cyclosporine, and a better history of patient survival.

Cyclosporine appears to have promise in the treatment of autoimmune diseases. It 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 cyclosporine are often required to suppress autoimmune disorders.

Adverse Effects

Compared with previously available therapy, the adverse effects associated with cyclosporine are much less severe but still worthy of concern. Nephrotoxicity, which can occur in up to 75% of patients, ranges from severe tubular necrosis to chronic interstitial nephropathy. This effect is generally reversible with dosage reduction. Vasoconstriction appears to be an important aspect of cyclosporine-induced nephrotoxicity. Hypertension occurs in 25% of the patients 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.

Corticosteroids

Corticosteroids, such as prednisone (*Deltasone, Meticorten*) and prednisolone (*Prelone, Delta-Cortef*), have been used alone or in combination with other agents in the treatment of autoimmune disorders and for the prevention of allograft rejection. However, the toxicity associated with their use necessitates prudent administration. Additional information on corticosteroids can be found in Chapter 60.

Although corticosteroids possess immunosuppressive properties, their real value is in controlling the inflammation that can accompany transplantation and autoimmune disorders. Virtually all phases of the inflammatory process are affected by these drugs. Corticosteroid therapy alone is successful in only a limited number of autoimmune diseases, such as idiopathic thrombocytopenia, hemolytic anemia, and polymyalgia rheumatica.

Tacrolimus

Tacrolimus (*Prograf*) is a second-generation immunosuppressive agent that has been approved for use in liver transplantation. Its efficacy for other transplantations is being evaluated. It has properties similar to those of cyclosporine except that weight for weight it is 10 to 100 times more potent. It is a macrolide antibiotic that selectively inhibits transcription of a specific set of lymphokine genes in T lymphocytes (e.g., IL-2, IL-4, and interferon-γ) and binds to cytoplasmic proteins in lymphocytes. Although the binding proteins (cytophilins) for cyclosporine and tacrolimus are different, they share similar functions in that the cytophilins are important for the intracellular folding of proteins. It is speculated that these proteins are important in regulating gene expression in T lymphocytes and that both drugs somehow interfere in this process.

Absorption of tacrolimus from the gastrointestinal (GI) tract is variable. It is extensively metabolized in the liver and excreted in the urine. As with cyclosporine, nephrotoxicity is its principal side effect.

Sirolimus

Sirolimus (*Rapamune*) is structurally related to tacrolimus. It is approved for use as an adjunctive agent in combination with cyclosporine for prevention of acute renal allograft rejection. It blocks IL-2-dependent T-cell proliferation by inhibiting a cytoplasmic serine–threonine kinase. This mechanism of action is different from those of tacrolimus and cyclosporine. This allows sirolimus to augment the immunosuppressive effects of these drugs.

Azathioprine

Azathioprine (*Imuran*) is a cytotoxic agent that preferentially destroys any rapidly dividing cell. Since immunologically competent cells are generally rapidly dividing cells, azathioprine is very effective as an immunosuppressive drug. Unfortunately, any cell that is replicating is a target for this action. This lack of specificity leads to serious side effects.

Azathioprine, in combination with corticosteroids, has historically been used more widely than any other drug in immunosuppressive therapy. It is classified as a purine antimetabolite and is a derivative of 6-mercaptopurine (see Chapter 56).

Mechanism of Action

Azathioprine is a phase-specific drug that is toxic to cells during nucleic acid synthesis. Phase-specific drugs are toxic during a specific phase of the mitotic cycle, usually the S-phase, when DNA synthesis is occurring, as opposed to cycle-specific drugs that kill both cycling and intermitotic cells.

Azathioprine is converted in vivo to thioinosinic acid, which competitively inhibits the synthesis of inosinic acid, the precursor to adenylic acid and guanylic acid. In this way, azathioprine inhibits DNA synthesis and therefore suppresses lymphocyte proliferation. This effectively inhibits both humoral and cell-mediated immune responses.

Absorption, Metabolism, and Excretion

Azathioprine is well absorbed following oral administration, with peak blood levels occurring within 1 to 2 hours. It is rapidly and extensively metabolized to 6-mercaptopurine, which is further converted in the liver and erythrocytes to a variety of metabolites, including 6-thiouric acid. Metabolites are excreted in the urine. The half-life of azathioprine and its metabolites in the blood is about 5 hours.

Clinical Uses

Azathioprine is a relatively powerful antiinflammatory agent. Although its beneficial effect in various conditions is principally attributable to its direct immunosuppressive action, the antiinflammatory properties of the drug play an important role in its overall therapeutic effectiveness.

Azathioprine has been used widely in combination with corticosteroids to inhibit rejection of organ transplants, particularly kidney and liver allografts. However, it is usually reserved for patients who do not respond to cyclosporine plus corticosteroids alone.

Azathioprine also has applications in certain disorders with autoimmune components, most commonly rheumatoid arthritis. It is as effective as cyclophosphamide in the treatment of Wegener's granulomatosis. It has largely been replaced by cyclosporine in immunosuppressive therapy. Relative to other cytotoxic agents, the better oral absorption of azathioprine is the reason for its more widespread clinical use.

Adverse Effects

The therapeutic use of azathioprine has been limited by the number and severity of adverse effects associated with its administration. Bone marrow suppression resulting in leukopenia, thrombocytopenia, or both may

occur. GI toxicity may be a problem. It is also mildly hepatotoxic. Because of its immunosuppressive activity, azathioprine therapy can lead to serious infections. It has been shown to be mutagenic in animals and humans and carcinogenic in animals.

Mycophenolate Mofetil

Mycophenolate mofetil (*CellCept*), in conjunction with cyclosporine and corticosteroids, has clinical applications in the prevention of organ rejection in patients receiving allogeneic renal and cardiac transplants. By effectively inhibiting de novo purine synthesis, it can impair the proliferation of both T and B lymphocytes. Following oral administration, mycophenolate mofetil is almost completely absorbed from the GI tract, metabolized in the liver first to the active compound mycophenolic acid, and then further metabolized to an inactive glucuronide.

Early clinical trials indicate that mycophenolate mofetil in conjunction with cyclosporine and corticosteroids is a more effective regimen than azathioprine in preventing the acute rejection of transplanted organs. GI side effects are most common.

Other Cytotoxic Drugs

Although azathioprine is the most popular cytotoxic drug used for immunosuppression, others have been employed. Among these is cyclophosphamide, a cycle-specific agent that acts by cross-linking and alkylating DNA, thereby preventing correct duplication during cell divisions. Methotrexate is a phase-specific agent that acts by inhibiting folate metabolism. It is highly toxic and appears to offer no advantages over azathioprine. Chlorambucil, an alkylating agent, has actions similar to those of cyclophosphamide. In contrast, its adverse effects are fewer in that alopecia and GI intolerance are almost never encountered. See Chapter 56 for further details of these agents.

Antibodies

Antiserum can be raised against lymphocytes or thymocytes by the repeated injection of human cells into an appropriate recipient, usually a horse. The use of such antiserum or the immune globulin fraction derived from it has been used to produce immunosuppression. Although antilymphocytic serum can suppress cellular and often humoral immunity against a variety of tissue graft systems, the responses are variable, particularly from one batch of serum to another.

Antithymocyte Globulin

Antithymocyte globulin (*Atgam*) is purified immune globulin obtained from hyperimmune serum of horses immunized with human thymus lymphocytes. It has been used successfully alone and in combination with azathioprine and corticosteroids to prevent renal allograft rejection. Although it has benefits when administered prophylactically, its use during rejection episodes may be its greatest value.

Antithymocyte globulin binds to circulating T lymphocytes in the blood, which are subsequently removed from the circulation by the reticuloendothelial system. This globulin also reduces the number of T lymphocytes in the thymus-dependent areas of the spleen and lymph nodes.

Since the preparations are raised in heterologous species, reactions against the foreign proteins may lead to serum sickness and nephritis. The concomitant use of corticosteroids may alleviate this response.

Muromonab-(CD3)

Muromonab-(CD3) (*Orthoclone OKT3*) is a mouse monoclonal antibody that is a purified IgG. It is used for the prevention of acute allograft rejection in kidney and hepatic transplants and as prophylaxis in cardiac transplantation. It is also used to deplete T cells in marrow from donors before bone marrow transplantation.

Muromonab-(CD3) alters the cell-mediated immune response by binding to the CD3 (cluster of differentiation antigen, T3) glycoprotein on T lymphocytes. This binding inhibits lymphocyte activation so that affected T cells cannot recognize foreign antigen and cannot participate in rejecting an organ graft. Within minutes of the first muromonab-(CD3) injection, total circulating T cells are rapidly depleted from the blood. They later reappear devoid of CD3 and antigen recognition complexes.

Adverse side effects include fever, pulmonary edema, vomiting, headache, and anaphylaxis. Neutralizing antibodies may develop over time and necessitate adjusting the dosage upward to compensate for the loss of therapeutic activity.

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 entered her 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.

INDIVIDUAL DRUGS USED TO STIMULATE THE IMMUNE SYSTEM

A number of disorders can be treated with *immuno-stimulating agents* (also known as biological response modifiers or immunomodulating agents); these drugs enhance the body's immune response. These conditions include immunodeficiency diseases, cancer, some types of viral and fungal infections, and certain autoimmune disorders. The drugs may work on cellular or humoral immune systems or both.

Immunostimulating agents are nonspecific; they cause general stimulation of the immune system. Among the agents capable of general potentiation of the immune system are extracts and derivatives from bacteria, yeast, and fungi. They also include a variety of peptides, cytokines, and synthetic compounds. In most cases, the pharmacology of these agents has not been well described. The most commonly used agents are discussed next.

Bacillus Calmette-Guérin

Bacillus Calmette-Guérin (BCG) is a viable attenuated strain of *Mycobacterium bovis*. Nonviable strains of the bacterium also have been shown to augment the immune response. The smallest active compound derived from BCG thus far has been identified as muramyl dipeptide. The T cell is a principal target for BCG. It also appears to stimulate natural killer cells, which in turn can kill malignant cells. It has been suggested that BCG cross-reacts immunologically with tumor cell antigens.

BCG immunotherapy has been most successful in the treatment of bladder cancers. It is instilled directly into the bladder, where it is held for 2 hours before urination.

The most dangerous complications of BCG therapy are severe hypersensitivity and shock. Chills, fever, malaise, immune complex, and renal disease are among the other side effects. The route of administration influences the nature of the side effects.

Levamisole

Levamisole (*Ergamisol*) was originally developed as an antihelminthic drug (see Chapter 54). It potentiates the stimulatory effects of antigens, mitogens, lymphokines, and chemotactic factors on lymphocytes, granulocytes, and macrophages. It has been shown to increase T cell–mediated immunity.

Levamisole has been used successfully in treating chronic infections. It also has been approved for use in combination with fluorouracil in the treatment of colorectal cancer.

Immune Globulin

Immune globulin is isolated from pooled human plasma either from donors in the general population or from hyperimmunized donors. It is used principally in the treatment of certain immune deficiencies. Standard immune globulin solutions contain a distribution of all subclasses, with antibody titers for most major bacterial, viral, and fungal pathogens.

Immune globulin, given intramuscularly or intravenously, is recommended in the treatment of primary humoral immunodeficiency, congenital agammaglobulinemias, common variable immunodeficiency, severe combined immunodeficiency, idiopathic thrombocytopenic purpura, and autoimmune hemolytic anemia. There are six licensed preparations of immune globulin.

The principal side effects are possible anaphylactoid reactions and severe hypotension.

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) are 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.

Few major side effects have been reported, especially with purer forms produced by genetic engineering. Crude thymic preparations have produced allergic side effects in some patients.

Cytokines

An exciting application of immunomodulating therapy is in the use of cytokines (*lymphokines, monokines*). As mentioned earlier in this chapter, immune cell function is regulated by cytokines produced by leukocytes or other supporting cells. With the advent of genetic engineering, cytokines can be produced in pure form and in large quantities.

Interleukin-2

IL-2 (*Proleukin*) is a cytokine that promotes the proliferation, differentiation, and recruitment of T and B lymphocytes, natural killer cells, and thymocytes. Human recombinant IL-2 is designated as rIL-2. rIL-2 binds to IL-2 receptors on responsive cells and induces proliferation and differentiation of T helper cells and T cytotoxic cells. It also can induce B-lymphocyte proliferation, activate macrophage activity, and augment the cytotoxicity of natural killer cells.

rIL-2 is administered systemically as an immunostimulating agent in patients with AIDS and to augment specific antitumor immunity. Patients with renal cell carcinoma or melanoma have been effectively treated with rIL-2 in combination with adoptive transfer immunotherapy. The latter refers to the injection of the patient's own cytokine-activated killer cells or tumor-infiltrating lymphocytes after they reside in tissue culture for several weeks in the presence of rIL-2.

Systemic administration of rIL-2 causes fever, nausea, vomiting, fatigue, and malaise. Other adverse affects include flushing, diarrhea, chills, rash, edema, symptomatic hypotension, and certain renal abnormalities. These tend to occur at increased dosage levels and are attenuated by reducing the dosage.

Myeloid Colony–Stimulating Factors

Recombinant granulocyte-macrophage colony–stimulating factor (GM-CSF) (*Sargramostim*) and granulocyte stimulating factor (G-CSF) (*Filgrastim*) are cytokines, or growth factors, that support the survival, clonal expansion, and differentiation of hematopoietic cells. These factors are normally produced in the body by monocytes, fibroblasts, and endothelial cells. GM-CSF induces bone marrow progenitor cells belonging to the granulocyte or macrophage lineage to divide and differentiate into mature cells. G-CSF induces the maturation of granulocyte progenitor cells.

In general these recombinant cytokines are indicated for acceleration of the recovery of circulating white blood cells in patients who have depressed hematopoiesis, as a result of either chemotherapy or congential disorders of hematopoiesis. A list of indications for the use of GM-CSF and G-CSF is provided in Table 57.2.

Results of several phase 1 and phase 2 clinical trials suggest that these cytokines are well tolerated. Adverse effects are those commonly observed following the administration of molecules produced by biotechnological

TABLE 57.2	Clinical Indications for the Use of Myeloid Colony–Stimulating Factors
G-CSF, GM-CSF	Autologous and allogenic bone marrow transplant
	HIV infections
	Primer for stem cell collection
	Acute myeloid leukemia
GM-CSF	Aplastic anemia
	Myelodysplasia
G-CSF	Congenital neutropenia
	Chemotherapy-induced neutropenia
	Cyclic neutropenia

means. They include diarrhea, asthenia, rash, malaise, fever, headache, bone pain, chills, and myalgia. Many of these effects can be ameliorated by the administration of analgesics and antipyretics.

Other Cytokines

Human recombinant interferon-α(rIFN-α) and rIL-1 also show promise as immunostimulators, principally as adjuvants in the treatment of viral and malignant disorders.

rIFN-α is produced by leukocytes and inhibits viral DNA and RNA replication. At lower doses, it can stimulate macrophages, T lymphocytes, and natural killer cell activity.

rIL-1 is produced by macrophages in the host and is necessary for activation and development of immune cells. Intravenous administration of rIL-1 is associated with the general augmentation of immune responses.

rIL-6 is a protein that stimulates lymphocyte and megakaryocyte proliferation. It is in clinical trials in patients with refractory cancer and myelodysplastic syndrome. Trials also are ongoing with rIL-3, a multipotent factor that stimulates the growth of monocytes, erythrocytes, neutrophils, and megakaryocytes.

Study QUESTIONS

1. An Rh-negative mother gives birth to an Rh-positive baby. This is the mother's first child. Is immunotherapy necessary?
   (A) Yes. The mother should receive Rho(D) immune globulin to prevent hemolytic anemia in future neonates.
   (B) Yes. The mother's immune system reacted against the baby's T cells. Thymosin should be given to augment the baby's cellular immunity.
   (C) Yes. The mother's immune system reacted against the baby's B cells. Fetal interferonγ should be given to augment the baby's humoral immunity.
   (D) No. Immunotherapy is not necessary, since this is the first child.
   (E) No. Immunotherapy would only have been necessary if the mother were Rh positive and baby Rh negative.

2. Cytotoxic agents such as azathioprine are effective immunosuppressants because they
(A) Bind to and inactivate circulating immunocomplexes
(B) Specifically inhibit IL-2 gene transcription
(C) Prevent the clonal expansion of T and B cells by inhibiting purine synthesis
(D) Induce the synthesis of antiidiotype antibodies
(E) Alkylate and cross-link DNA, preventing blastogenesis

3. Interleukin-2 can be beneficial in the treatment of AIDS because it can
(A) Attach to the HIV virus, making it more susceptible to phagocytosis
(B) Bind to IL-2 receptors on responsive immune cells and stimulate the production of T helper and T cytotoxic cells.
(C) Cross-link antibodies on mast cell surfaces leading to degranulation.
(D) Activate the complement cascade by binding to the C5a fragment.
(E) Inhibit T suppressor cell activity and thereby stimulating the immune response

4. A 4-year-old boy has significantly reduced levels of IgA, IgM, IgD and IgE in his blood. Testing demonstrates that he did not develop the appropriate antibody titer following standard childhood vaccinations. The most probable cause of these deficiencies is
(A) Deficiency in macrophage function that is preventing the proper presentation of antigens to T cells
(B) Lack of a specific component of the complement cascade
(C) Alcohol abuse by the mother during pregnancy
(D) A primary immunodeficiency disease that is blocking the maturation of B cells into plasma cells
(E) An autoimmune disease targeted at basophil surface receptors

5. Which of the following best describes the side effects of cyclosporine therapy?
(A) Leukopenia, hypotension, hemolytic anemia
(B) Nephrotoxicity, neurotoxicity, hirsutism
(C) Thrombocytopenia, hypokalemia
(D) Hemorrhagic cystitis, hypoglycemia
(E) Increase circulating immune complexes, cardiac arrhythmia

ANSWERS

1. **A.** An Rh-negative mother can develop antibodies against the Rh antigen if she is exposed to the blood of an Rh-positive baby during pregnancy or birth. If no therapy is given, hemolytic anemia can occur in future Rh-positive babies. Rho(D) immune globulin contains antibodies against the Rh antigen. Administered to the mother, it will destroy any red blood cells from the baby that entered her blood, preventing the mother from developing an immune response to the Rh antigen.

2. **C.** Azathioprine is a phase-specific cytotoxic agent that functions by inhibiting purine synthesis. The other answers are wrong because azathioprine is nonspecific, is not an alkylating agent, has no effect on immune complexes, and does not induce antibody synthesis.

3. **B.** IL-2 stimulates the immune system by binding to the IL-2 receptors on responsive immune cells, causing differentiation and proliferation of T helper and T cytotoxic cells. It has no direct effect on the HIV virus, complement. or basophils.

4. **D.** The boy has significantly reduced serum antibody levels and a reduced ability to mount an antibody response to childhood vaccinations. The most probably cause is a primary immunodeficiency disease affecting humoral immunity.

5. **B.** The primary side effect of cyclosporine therapy is nephrotoxicity, occurring in up to 75% of cases. Unwanted hair growth and neurotoxicity are also commonly noted. The other answers are wrong because cyclosporine therapy is associated with hypertension, hyperkalemia, and hyperglycemia. There are no references to cyclosporine having cardiac or immune complex effects or causing hemorrhagic cystitis.

SUPPLEMENTAL READING

Campistol JM and Grinyo JM. Exploring treatment options in renal transplantation: The problems of chronic allograft dysfunction and drug-related nephrotoxicity. Transplantation 2001;71:SS42–SS51.

Gorantla VS et al. Immunosuppressive agents in transplantation: Mechanisms of action and current anti-rejection strategies. Microsurgery 2000;20:420–429.

Graham RM. Cyclosporine: Mechanism of action and toxicity. Cleveland Clin I Med 1994;61:308–313.

Kupiec-Weglinski JW. New Immunosuppressive Modalities and Anti-rejection Approaches in Organ Transplantation. Boca Raton, FL: CRC, 1994.

Nakamura T and Matsumoto K. Growth Factors: Cell Growth, Morphogenesis, and Transformation. Boca Raton, FL: CRC, 1994.

Nicola NA (ed.). Guidebook to Cytokines and Their Receptors. New York: Oxford University Press, 1995.

Yin EZ, Frush DP, Donnelly LF, and Buckley RH. Primary immunodeficiency disorders in pediatric patients: Clinical features and imaging findings. Am J Roentgenol 2001;176:1541–1552.

CASE Study   Adverse Reactions to Transplantation

Four weeks after receiving a bone marrow transplant, Mary Smith developed jaundice and a skin rash on her hands, feet, and face. She also had occasional episodes of vomiting and diarrhea. Clinical chemistry results showed her serum liver enzymes (LDH, ALT) and bilirubin level to be elevated. What is the most likely cause of Mary's symptoms and what is the best therapy?

ANSWER: Ms. Smith has an acute graft-versus-host (GVH) reaction. Such reactions usually occur when immunologically competent cells are introduced into an immunocompromised host. When they develop, it is usually within 100 days following transplant. In choosing tissues and organs for transplantation, the HLA antigens of donors and patients are matched as closely as possible to decrease the risk of rejection. However many minor antigenic markers that can cause immunological incompatibility differ between individuals. In this case, T lymphocytes from the donor's bone marrow are attacking her skin, liver, stomach, and intestines. Patients with GVH reactions are already receiving cyclosporine or other immunosuppressive therapy. When a GVH reaction is diagnosed, treatment with corticosteroids, such as prednisone and prednisolone, is usually added.