

26. Immunomodulation and immunotherapy: Drugs, cytokines, cytokine receptors, and antibodies

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The preceding chapters in this primer have provided an overview of the immune response that serves as a background for understanding potential sites for immune modulation and immunotherapy. A number of soluble growth and activation factors are released from various cell populations involved in the immune response. They play vital roles in the initiation, propagation, and regulation of immunologic responses. Pharmacologic immunomodulators include suppressive and stimulatory agents. Immunosuppressive therapies include antimetabolites, cytotoxic drugs, radiation, adrenocortical glucocorticosteroids, immunophilins, and therapeutic antibodies. The field of clinical immunostimulation is emerging as an important therapeutic modality for a number of immunodeficiency diseases, chronic viral infections, and cancer. These compounds will be discussed in terms of general principles, molecular targets, major indications, and adverse effects. (*J Allergy Clin Immunol* 2003;111:S720-32.)

Key words: *Immunomodulation, immunosuppressive, cytokines, monoclonal antibodies, biological response modifiers, autoimmunity, immunodeficiency, transplantation, glucocorticosteroids, immunophilins*

An impressive group of therapies that alter immunologic function for the treatment of human disease has been developed. Modalities include irradiation, cytotoxic chemotherapeutic agents, and glucocorticosteroids (GCS) that have been available for many years. They induce broad and potent immunosuppressive effects, as well as frequent, sometimes fatal side effects. Advances in clinical immunomodulation include dosing modifications of classic preparations and implementation of new medications.

Basic immunobiologists have elucidated mechanisms of immunologic specificity, recognition, activation, regulation, and tolerance induction that depend on the interactions of many cell types and their products. These discoveries have led to the development of therapies that target components whose altered function results in more focused effects, which may permit selective modulation of immunologic balance without severe side effects (Fig 1). Currently available agents include new classes of nonspecific immunosuppressive therapies and those aimed at specific cells, cytokines, or cytokine receptors.

Abbreviations used

AITP:	Autoimmune thrombocytopenia purpura
ANCA:	Anti-neutrophil cytoplasmic antibodies
AP-1:	Activating protein-1
CSA:	Cyclosporine A
CRS:	Cytokine release syndrome
COX-2:	Cyclooxygenase
FDA:	Food and Drug Administration
GCS:	Glucocorticosteroids
GR:	Glucocorticosteroid receptor
GRE:	Glucocorticoid response elements
GVHD:	Graft-versus-host-disease
HCT:	Hematopoietic cell transplantation
ICAM:	Intercellular cell adhesion molecule
IMDP:	Inosine monophosphate dehydrogenase
INF:	Interferon
ITIM:	Immunoregulatory tyrosine-based inhibition motif
IVIG:	Intravenous immunoglobulin
MMF:	Mycophenolate mofetil
mTOR:	Target of rapamycin
NF- κ B:	Nuclear factor kappa B
NF-AT:	Nuclear factor of activated T-cells
RCC:	Renal cell carcinoma
RSV:	Respiratory syncytial virus
RSV-IGIV:	Respiratory syncytial virus immune globulin intravenous
TEN:	Toxic epidermal necrolysis
TBI:	Total body irradiation
TNF:	Tumor necrosis factor
VZIG:	Varicella-zoster immune globulin
VZV:	Varicella-zoster virus

Immunomodulation also includes therapies that boost an individual's defenses by providing either physiologic or supraphysiologic dosages of exogenous cytokines to treat chronic viral infections and malignancies. Another group of agents stimulate hematopoietic recovery in patients suffering from cytopenias resulting from disease or therapy-related bone marrow suppression. Monoclonal antibodies and hybrid molecules are important additions; the latter combine the specificity of the immune therapy with a cytotoxic chemical or radiation effect. Recently approved medications are rapidly becoming standard primary or adjunctive treatments for patients who are managed by a range of clinicians and all transplant surgeons. This chapter will discuss those therapies available for human use at the time of this publication. The future is bright for clinical immunotherapy, as the basic understanding of human immunophysiology reaches a new scope and dimension.

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0091-6749/2003 \$30.00 + 0

doi:10.1067/mai.2003.146

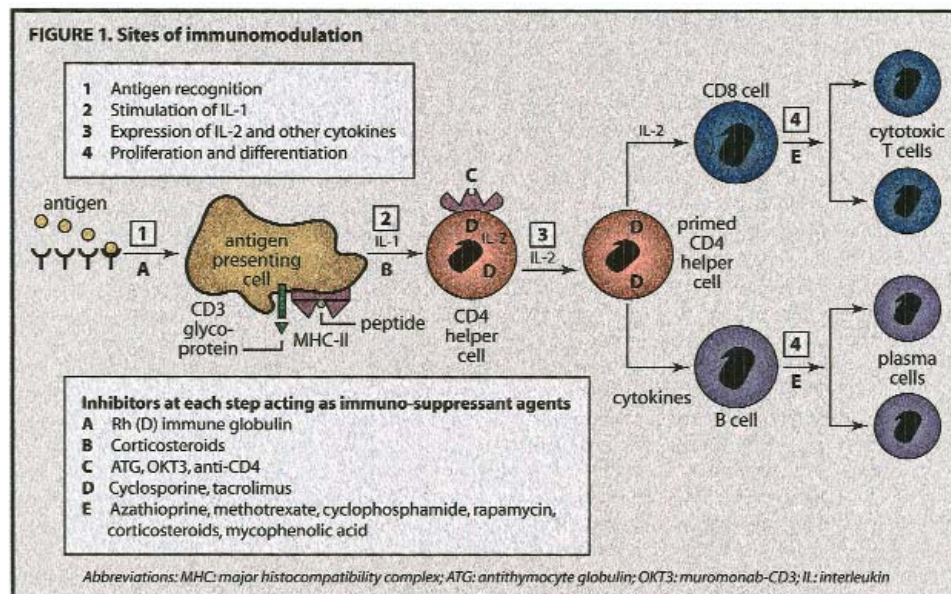


FIG 1. Sites of immunomodulation. Steps of both antibody and cell-mediated immune responses to antigens (such as may be involved in autoimmune disease) are numbered in the figure. Examples of different immunomodulators that can suppress these steps are indicated in letters. For example, Rh (D) immune globulin (A) prevents the sensitization of the immune system by attaching to foreign red blood cells at the initial step (Step 1) of antigen-presenting cells. Corticosteroids (B) decrease the reactivity of CD4⁺ cells with antigen-presenting cells at Step 2. Anti-T-cell antibodies (C) inactivate CD4⁺ T-cells (Step 3). Immunophilins act within the cells (activated CD4⁺ and CD8⁺ T-cells) to reduce their activation state (Step 3). Antimetabolites and other drugs interfere with the effector function of cytotoxic CD8⁺ T cells and activated B cells that cause autoimmune disease, for example (Step 4).

IRRADIATION AND DRUGS

Irradiation and chemotherapeutic cytotoxic pharmaceuticals possess potent immunosuppressive activities that make them candidates for the treatment of diseases characterized by disordered immunologic function. Irradiation (total body or localized) and cytotoxic or antimetabolite drugs, such as azathioprine, methotrexate, and cyclophosphamide, are the predominant modalities in common use at this time for a variety of immunomodulating purposes. Mycophenolate mofetil is a recent addition to this group of drugs.

Irradiation

High-dose, total body irradiation (TBI) has profound immunosuppressive effects that are used for the conditioning of certain patients before hematopoietic cell transplantation (HCT). After TBI, 80% of lymphocytes undergo prompt intermitotic death. Among these are B lymphocytes and the precursors to all T-cell subpopulations; in addition, the homing activity of cells is affected.¹ TBI prevents primary immune responses to neoantigens more effectively than modifying responses to recall antigens. Alternative approaches include total lymphoid irradiation that is effective for the treatment of Hodgkin's disease, solid organ graft rejection, and severe rheumatoid arthritis, and as a component of conditioning prior to HCT. Local irradiation, including regional lymph node irradiation, produces lymphopenia and decreased delayed hypersensitivity responses, but does not increase susceptibility to infection.²

Azathioprine

Azathioprine is hepatically metabolized to the purine analogue 6-mercaptopurine after oral administration. This metabolite incorporates into DNA, which results in death of rapidly dividing cells of the bone marrow and intestine. Six-mercaptopurine prevents or minimizes the immune-mediated rejection of transplanted organs and modulates autoimmune diseases, including rheumatoid arthritis, Crohn's disease, ulcerative colitis, and chronic graft-versus-host disease (GVHD) after HCT.^{3,4} Therapeutic immunosuppression occurs at doses of 1.5 mg/kg, which minimally suppresses leukocyte counts in most people. Long-term therapy is associated with an increased risk of squamous carcinomas of the skin, lymphoma, and bacterial and opportunistic infections.

Methotrexate

Methotrexate inhibits dihydrofolate reductase, which results in accumulation of inactive oxidized folates and cessation of nucleotide synthesis. This activity primarily kills cells that are in S-phase (DNA synthesis); nonproliferating cells are resistant. Methotrexate also inhibits macrophage activation, as demonstrated in an animal model of adjuvant arthritis.⁵ Methotrexate is given to humans to prevent GVHD after HCT and for the treatment of rheumatoid arthritis, systemic lupus erythematosus (SLE), and psoriasis.⁶ Weekly oral methotrexate has been suggested to have a steroid-sparing effect in severe asthmatics; however, the effectiveness of this is controversial.^{7,8} Methotrexate has provided short-term efficacy

for the treatment of juvenile rheumatoid arthritis.⁹ Risk factors for enhanced hematologic toxicity include renal insufficiency, concomitant nonsteroidal anti-inflammatory and trimethoprim-sulfamethoxazole administration, intravascular volume depletion, or folate deficiency. Long-term use is associated with hepatic fibrosis that leads to cirrhosis in some patients, a complication that is not uniformly predicted by hepatocellular enzyme elevation. Periodic liver biopsy should be considered for long-term recipients of the drug.¹⁰ Methotrexate is teratogenic and should be avoided, if possible, in pregnant women; but it does not appear to be carcinogenic.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that forms covalent bonds with DNA, thereby leading to DNA fragmentation, mutations, and cell death. It suppresses cellular immunity and inhibits antibody and autoantibody production. The primary use for cyclophosphamide is as conditioning therapy before HCT and for the treatment of SLE and vasculitis. A single daily dose is typically used for the treatment of Wegener's granulomatosis, whereas monthly "pulse" therapy, usually in combination with maintenance oral prednisone, is the approach for the treatment of SLE with nephritis.^{11,12} Adverse effects include leukopenia, sterility, hemorrhagic cystitis, and malignancy, including leukemias and transitional cell carcinoma. A thorough review of these potential effects should be undertaken with the family and documented in the medical record before treatment. Consideration of storage of sperm or ova should be raised with young adults before therapy.

Mycophenolate mofetil

Mycophenolate mofetil (MMF) is an ester of mycophenolic acid that inhibits the enzyme inosine monophosphate dehydrogenase (IMDP), thus inhibiting the *de novo* pathway of guanosine nucleotide synthesis, without incorporating into DNA. T- and B lymphocytes are critically dependent on *de novo* purine synthesis for DNA replication, whereas other cell types rely on nucleoside salvage pathways. Therefore, MMF exposure results in potent cytostatic effects on T- and B lymphocytes. MMF inhibits T-cell proliferation after mitogen and allogeneic stimulation, inhibits antibody production by B lymphocytes, and prevents glycosylation of adhesion proteins.¹³ The latter effect inhibits recruitment of lymphocytes to inflammatory foci. It is used to prevent organ rejection in renal, cardiac, and hepatic allotransplant recipients, and is usually given in conjunction with GCS and cyclosporine.^{14,15} It also is being investigated for the treatment of several autoimmune diseases.

Glucocorticosteroids

GCS are extremely potent, anti-inflammatory/immunosuppressive hormones; their actions are mediated by a variety of mechanisms that alter cell numbers and function. Steroid molecules interact with an intracytoplasmic glucocorticosteroid receptor (GR) that migrates into the nucleus,

where the activated GR complex binds to DNA sequences known as glucocorticoid response elements (GRE). This process impacts target gene transcription.¹⁶ Glucose metabolism is mediated by enhancement or inhibition of gene transcription. Anti-inflammatory effects of GCS result from the inhibition of transcription by direct GRE-DNA binding or by the production of proteins that have inhibitory effects on target gene transcription.¹⁷ Pro-inflammatory cytokines IL-1, IL-2, IL-6, IL-8, interferon (IFN)- γ and tumor necrosis factor (TNF)- α are inhibited. GCS enhance the production of lipocortin, which inhibits phospholipase A₂, interrupting arachidonic acid metabolism at the membrane level.¹⁷ This results in broad and potent reductions in leukotriene synthesis, which partially mediates the anti-asthmatic activity. GCS inhibit cyclooxygenase gene (COX-2) transcription, a rate-limiting enzyme for the production of prostaglandins, whereas IL-1 opposes this action. Collagenase, an enzyme that degrades tissue at sites of inflammation, is inhibited at the transcription level by binding of the GR complex to the proto-oncogene product, c-JUN, which is a component of the activating protein-1 (AP-1) transcription factor complex. AP-1 activity is then downregulated, which prevents collagenase gene transcription.¹⁸ Finally, GCS inhibit nitric oxide synthetase, which decreases production of nitric oxide, a potent vasodilator and mediator of inflammation.¹⁹ The biomedical effects of this broad inhibition of proinflammatory mediators are the reduction of tissue destruction, vasodilatation, vascular permeability, and acute phase reactivity. GCS alter the circulating number and function of neutrophils, eosinophils, macrophages, and lymphocytes.²⁰ Neutrophils are increased in the circulation, but are reduced at sites of inflammation by glucocorticoid-mediated downregulation of endothelial adhesion molecules, intercellular cell adhesion molecule (ICAM), and endothelial leukocyte adhesion molecule-1. Activation of neutrophils is reduced, at least in part, by glucocorticoid-mediated IL-8 inhibition. Eosinophil adherence and degranulation are inhibited. Monocyte-mediated effects are inhibited by the interference with recruitment, Fc-receptor function, antigen processing, and major histocompatibility complex class II and IL-1 production. Lymphocyte traffic is rerouted from recirculating to nonrecirculating pools in the lymph nodes and bone marrow. Immature lymphocytes and thymocytes are susceptible to glucocorticoid-induced apoptosis in experimental models. T-cell proliferation to soluble and cellular antigens and production of IL-2 is inhibited. B cells are redistributed, but immunoglobulin production is not directly inhibited, although serum IgG levels may be lower in subjects treated with GCS resulting from cytokine-mediated pathways or increased immunoglobulin metabolism. Thus, it is important to recognize that steroid-dependent asthmatics may have low total IgG levels because of increased metabolism, rather than decreased production. This makes immunoglobulin replacement therapy an uncommon necessity for the treatment of severe asthma.

The diverse anti-inflammatory and immunosuppressive activities of GCS translate into potent clinical effects for the treatment of allergic, dermatologic, and autoim-

TABLE I. Relative pharmacologic potencies, equivalent dosage, and biologic and plasma half-life ($t_{1/2}$) of GCS preparations

	Anti-inflammatory potency*	Equivalent pharmacologic dose (mg)	Mineralocorticoid potency†	Plasma $t_{1/2}$ (hr)	Biologic $t_{1/2}$ (hr)	HPA axis suppression (mg)‡
Hydrocortisone	1	20	2	1.5	8-12	20-30
Cortisone	0.8	25	2	1.5	8-12	20-35
Prednisone	2.7	5	1	2.7	12-36	7.5
Prednisolone	4	5	1	2.75	12-26	7.5
Methylprednisolone	5	4	0	3	12-26	7.5
Triamcinolone	5	4	0	4.2	24-48	5-7.5
Dexamethasone	30	0.75	0	5	36-54	1-1.5

*Relative to hydrocortisone, which is assigned a value of 1.

†Range, 0-4.

‡Daily dose that usually leads to HPA suppression.

mune diseases. GCS are used to prevent GVHD and graft rejection in HCT and solid organ allograft recipients, respectively. GCS are paradoxically used in conjunction with antimicrobial therapy for the treatment of *Pneumocystis carinii* pneumonia, in which case their anti-inflammatory activity improves oxygenation and decreases clinical progression to ventilator dependence, whereas the antimicrobial drug eliminates the organism.

Multiple systemic GCS are available for clinical use, and a large variety of agents may be topically applied to the skin, conjunctiva, nasal mucosa, rectal mucosa, or delivered to pulmonary tissue by inhalation. The plasma half-life of GCS is the time required for disappearance into tissues of half the circulating plasma concentration. The biological half-life is a measure of the duration of anti-inflammatory activity, which approximates the duration of hypothalamic-pituitary suppression. Tissue effects are estimated, therefore, by metapyrone testing and may persist long after the GCS have disappeared from the circulation. The glucocorticoid potency of cortisol is dependent on its 11-beta hydroxyl group; 11-keto compounds (cortisone and prednisone) must be converted to the corresponding 11-beta hydroxyl compound to be active. Prednisolone or methylprednisolone, 11-beta hydroxyl compounds, may be preferred for patients with impaired liver function or congestive heart failure.

GCS can be divided into three groups, based on plasma and biologic half-lives: short-acting, intermediate-acting, and long-acting drugs. Hydrocortisone is a short-acting form of GCS that is assigned an anti-inflammatory and endocrine potency of 1 and a sodium retaining potency of 2 (Table I). Prednisone, prednisolone, and methylprednisolone are intermediate-acting agents and have less sodium retention than hydrocortisone. The long-acting preparations are virtually devoid of sodium-retaining activity and include dexamethasone, triamcinolone acetonide, fluticasone propionate, budesonide, and beta-methasone dipropionate. Equivalent potencies and plasma half-lives of the more important preparations are included in Table I.

Giving GCS in multiple doses daily, such as every 6 to 8 hours, maximizes anti-inflammatory effects and adverse side effects. Less effective (and less toxic) regimens include single daily morning administration and alternate-

morning administration. A relatively recent modification is the administration of a large bolus or "pulse" dose (ie, sol-medrol, 15-30 mg/kg) daily for 1 to 3 days, at monthly intervals, to achieve potent anti-inflammatory activity while limiting daily chronic exposure. The efficacy of such treatment has been evaluated in controlled studies with patients with rheumatoid arthritis, SLE nephritis, and interstitial lung disease. A general guide for clinicians treating allergic, inflammatory, and autoimmune conditions is to use sufficient quantities to control the disease, then reduce to the lowest dose necessary to maintain disease remission while limiting side effects. Adverse effects are minimized by alternate-day oral administration, pulse therapy, the use of topical preparations, and the incorporation of adjunctive nonsteroidal anti-inflammatory/immunosuppressive medications. These strategies may permit the avoidance of the toxicities that universally occur in patients given supra-physiologic dosages of daily exogenous GCS.²¹

The predominant serious side effects in adults are the development of glucose intolerance, weight gain, osteoporosis, hypertension, gastritis, cataracts, and, occasionally, aseptic necrosis of the large joints, psychogenic effects, and susceptibility to viral, fungal, and mycobacterial infections. It is important to recognize that long-term hypothalamic pituitary axis suppression occurs. Long-term GCS recipients should be treated with higher dosages (ie, two to three times maintenance) before major surgical procedures. Fatal Addisonian crises after general surgical procedures during steroid withdrawal occur, albeit rarely. Growth failure complicates GCS use in children. The probability that most patients will experience iatrogenic complications with extended use underscores the clinician's responsibility to inform patients of these potential outcomes. Many physicians request that patients sign consent that these issues have been discussed before therapy is initiated, but this practice is not universal.

Immunophilin-binding agents

Cyclosporine, tacrolimus, and sirolimus, derived from fungi, are important immunosuppressive medications that inhibit T-cell activation through a series of calcium-dependent signal events involved in cytokine gene transcription. These compounds not only play especially important roles in suppression of solid organ allograft

TABLE II. Indications for the use of recombinant interferon in human illness

<u>Interferon alpha-2a</u>	<u>Interferon alpha-2b</u>
<u>Interferon alpha-n</u>	Malignant melanoma, Condyloma acuminata
Malignant melanoma	Follicular lymphoma
Follicular lymphoma	AIDS-related Kaposi's sarcoma
AIDS-related Kaposi's sarcoma	Condylomata acuminata
Condylomata acuminata	Chronic hepatitis B
Chronic hepatitis C	Chronic hepatitis C
Chronic myelogenous leukemia	
<u>Interferon beta-1b</u>	
Relapsing-remitting multiple sclerosis (ambulatory patients)	
<u>Interferon gamma</u>	
Chronic granulomatous disease	
Idiopathic pulmonary fibrosis	
Recurrent mycobacterium avium complex infection	

rejection, they are the mainstays of GVHD prevention after HCT and are increasingly useful for the treatment of autoimmune conditions.

Cyclosporine (CsA) is a cyclic hexapeptide that blocks the calcium-dependent signal-transduction pathway emanating from the T-cell receptor, thereby inhibiting the activation of helper T cells. Tacrolimus (FK506) differs structurally from CsA but also interferes with T-cell receptor-dependent cell activation. Upon entry into the cells, these compounds form tight complexes with cytosolic receptors known as immunophilins, which subsequently bind to calcineurin, inhibiting its phosphatase activity. This prevents the dephosphorylation and nuclear translocation of the cytoplasmic subunit of the nuclear factor of activated T cells (NF-AT), rendering it incompetent. CsA and tacrolimus inhibit IL-2, IL-3, IL-4, INF- γ , granulocyte-macrophage colony-stimulating factor, and TNF- α production. Transcriptional factors NF-AT, nuclear factor kappaB (NF- κ B), and PU-box are inhibited. T-cell receptor-mediated apoptosis of lymphocytes and thymocytes is augmented by tacrolimus but not CsA, which represents an additional mechanism by which immunologic tolerance to allografts is achieved.^{22,23}

CsA is used clinically to prevent GVHD after bone marrow transplantation and graft rejection of solid organ transplants. CsA is also effective for the treatment of psoriasis, ocular disease associated with Behcet's disease, endogenous uveitis, atopic dermatitis, rheumatoid arthritis, Crohn's disease, nephritic syndrome, aplastic anemia, pure red cell aplasia, polymyositis/dermatomyositis, pyoderma gangrenosum, and severe asthma.²⁴⁻²⁶ Tacrolimus is used to promote solid organ tolerance, and clinical trials for several autoimmune conditions are in progress. The use of CsA and tacrolimus are complicated by the fact that absorption can be somewhat erratic, blood levels need to be monitored, multiple drugs that are metabolized by hepatic cytochrome p450 alter blood levels, and major clinical toxicities exist. Adverse effects include nephropathy, hypertension, diabetes mellitus, susceptibility to infection, development of malignancies, and posttransplant lymphoproliferative disorder.²⁷ Tacrolimus is associated with less hypertension and less concomitant glucocorticosteroid requirement in renal transplant recipients,

but a higher frequency of moderate to severe neurotoxicity in liver transplant patients with hepatitis C.

Sirolimus (rapamycin) is a macrocyclic lactone produced by *Streptomyces hygroscopicus* that inhibits, by a distinctive mechanism, T-lymphocyte activation and proliferation that occurs in response to antigenic and cytokine stimulation. Sirolimus binds intracellularly to the immunophilin, FK binding protein-12, which becomes an immunosuppressive complex. This complex binds to and inhibits the activation of the mammalian regulatory kinase, known as the target of rapamycin (mTOR).²⁷ This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G₁ to the S phases of the cell cycle. Sirolimus is indicated for the prophylaxis of organ rejection in patients receiving renal transplants, and possibly as a treatment for steroid-refractory acute GVHD therapy.

CYTOKINES

Hematopoietic growth factors

Hematopoietic growth factors for clinical use, including erythropoietin, granulocyte colony stimulating factor, and granulocyte/monocyte colony stimulating factor, are glycoproteins produced by recombinant DNA technology. These compounds have revolutionized the treatment of iatrogenic anemia and leukopenia and have their most widespread use in patients undergoing chemotherapy or transplantation for hematologic diseases and malignancies, those with anemia associated with chronic renal failure, and those requiring nucleoside analogue antiretroviral therapy.²⁸⁻³¹ Recently approved preparations have longer durations of action that make weekly or even bimonthly administration possible.

Interferons

Interferons for therapeutic use consist of recombinant DNA products that are available for intramuscular, subcutaneous, intralesional, or intravenous injection.³² The biological activities mimic those of the naturally occurring endogenous molecules that are produced and secreted by white blood cells in response to viral infections and for immunologic activation. This family of molecules

TABLE III. Therapeutic antibodies and cytokine receptors for immunomodulation and immunotherapy

Therapeutic agent	Proprietary	Target	Major indications	Adverse effects
Polyclonal antibodies				
Intravenous immunoglobulin	Multiple* Fc receptors Idiotypes	Organisms Post BMT CLL Pediatric AIDS ITP Kawaski Disease Neurological diseases	Immunodeficiencies	Anaphylactoid
Rh (D) immune globulin	Rhogam	D antigen	Rh-neg mothers	Minimal
Antithymocyte globulin	Atgam Thymoglobulin	Thymocytes	Aplastic anemia Organ rejection	Serum sickness Opportunistic infection
Varicella-zoster immune globulin	VZIG	Recently exposed subjects	Modify course of disease	Minimal
RSV immune globulin	RSV-IGIV	Respiratory-compromised subjects	Prevention during RSV season	Minimal except in children with cyanotic heart disease
Monoclonal antibodies				
RSV monoclonal antibody (palivizumab)	Synagis	Respiratory-compromised subjects	Prevention during RSV season	FDA approval pending
Muromonab-CD3	OKT3	CD3 lymphocytes	Organ rejection	Cytokine release syndrome
Infliximab	Remicade	TNF-alpha	RA, Crohn's Mycobacterial infection	Lupus-like syndrome
Alemtuzumab	Campeth-1H	CD52+ cells	Refractory CLL Opportunistic infection	Lymphopenia
Rituximab	Rituxin	CD20+ cells	NHL	Opportunistic Infection
Ibritumomab tiuxetan	Zevulin	CD20+ cells	Refractory NHL	Opportunistic Infection
Omalizumab	rhumAb-25	IgE-Fc binding domain	Steroid-dependent asthma	Possible IgG antibodies
Cytokine receptors				
Etanercept	Enbrel	TNF-alpha	RA	Injection site soreness; bone marrow suppression
Anakrina	Non-glycosylated form of IL-1Ra	IL-1	RA	Injection site soreness
Denileukin diftitox		IL-2	No established dose	

BMT, Bone marrow transplant; CLL, chronic lymphocytic leukemia; ITP, idiopathic thrombocytopenic purpura; RA, rheumatoid arthritis; NHL, non-Hodgkin's lymphoma.

*Multiple brands from different vendors.

was named for their capacity to "interfere" with in vitro infectivity of virions into mammalian cells. INF binds to the cell membrane and initiates a complex sequence of intracellular events, which include induction of enzymes, inhibition of cell proliferation, enhancement of phagocytosis by monocytes/macrophages, and augmentation of specific cytotoxicity of lymphocytes for target cells.³³ These in vitro effects do not exactly correlate with clinical results; however, they correctly predict that these compounds modulate a wide array of clinical disease immunopathophysiology. INF- α -2b, INF- β , and INF- γ have Food and Drug Administration-approved indications for a number of proliferative conditions and viral infections, as listed in Table II.³⁴ The administration of particular preparations is associated rarely with hypersensitivity reactions (eg, urticaria, angioedema, bronchoconstriction, anaphylaxis). Common side effects include fever, transient skin rashes, flulike symptoms, and bone marrow suppression. Thirty percent of patients experience neuropsychiatric symptoms, most commonly, depression. Rarely, patients experience autoimmune dis-

orders, ischemic events, and infections. Some patients with psoriasis experience disease exacerbations. Concomitant administration of theophylline and interferon alpha results in 100% increases in theophylline levels.

IL-2

IL-2, described as a T-cell growth factor in 1976, stimulates growth of T lymphocytes from normal human bone marrows.^{35,36} The gene from IL-2 was discovered in 1983, which made it possible for large-scale production by gene expression in *Escherichia coli*; the product is biologically and functionally similar to natural IL-2. Parenterally administered IL-2 is associated with a broad array of measurable changes in immunologic function that are summarized in a recent review.³⁷ IL-2 is FDA-approved for metastatic renal cell carcinoma (RCC). Approximately 15% to 20% of patients experience an objective response with therapy. The complete response rate is 5% to 7%, and about 80% of these complete responders will experience response duration of greater than 2 years. Toxicity of high-dose IL-2 therapy is significant, although treatment-

TABLE IV. Immunomodulatory mechanisms of action of IVIG

Fc receptor blockade or modulation
Fc receptor blockade of reticuloendothelial cell system and mononuclear phagocytes
Competitive interaction of IVIG with circulating IgG-sensitized platelets for Fc receptor on macrophages
Soluble Fcγ receptors compete with membrane Fc receptors (RES) for circulating IgG-sensitized platelets
Immunomodulation
Enhancement of T-cell suppressor function
Inhibition of B-cell function and/or antigen processing cells
Neutralization or binding of autoimmune antibodies by anti-idiotypic antibodies in the IVIG leading to restoration of idiotype-anti-idiotypic network
Inhibition of complement uptake on target tissues; prevent complement-dependent immune damage to tissue and cells
Inhibition of cytokine/interleukin production/action
Neutralization of bacterial enterotoxin superantigens
Inhibition of Fas-mediated cell death by Fas blocking antibodies in the IVIG

related mortality of systemic IL-2 therapy is less than 1%. These toxicities include hypotension requiring pressors, major organ failure, myocardial infarction, and potentially fatal systemic capillary leak.³⁸ Fisher reported long-term follow-up of the original cohort of 255 RCC patients treated with high-dose IL-2. The median response duration was 54 months (range, 3-131 months). The median duration for complete responders was not reached, but was greater than or equal to 80 months (range, 7-131 months). The median survival time for all 255 patients was 16.3 months, with 10% to 20% estimated to be alive at 5 to 10 years after treatment.³⁹

THERAPEUTIC ANTIBODIES

Intravenous immunoglobulin (polyclonal): Immune replacement therapy and immunomodulation

Immunoglobulin has been available for intravenous administration since 1981, and this mode of therapy has essentially replaced the use of intramuscular preparations for the treatment of immunodeficiency diseases. Intravenous immunoglobulin (IVIG) is prepared by cold ethanol-fractionation of plasma from multiple donors (10,000 to 60,000), followed by processes that remove antibody aggregates and inactivate potential viral pathogens. Preparations are usually supplied as 5% or 10% protein solutions. Ninety-five to 99% of the IVIG is IgG, with trace amounts of IgA and IgM. IgG subclass distribution is similar to that of normal serum. Some products that contain very low amounts of IgA may be beneficial in patients with complete IgA deficiency and IgE anti-IgA antibodies to minimize the risk of IgA sensitization and possible anaphylactic reactions.⁴⁰ All current preparations are essentially equivalent and are selected on the basis of cost, availability, and convenience, for example, lyophilized versus a liquid form.

Immune replacement therapy. IVIG is indicated as replacement therapy for patients with primary immunodeficiency diseases who have deficient antibody production (Table III). Infusions are given every 3 to 4 weeks at a dose of 400 to 600 mg/kg to achieve a trough IgG level greater than 500 mg/dL, a level that is correlated with reductions in

infection frequency.⁴¹ Quartier and associates performed a retrospective study of the clinical features and outcomes of 31 patients with X-linked agammaglobulinemia receiving replacement IVIG therapy between 1982 and 1997.⁴² Early treatment with IVIG and the achievement of a trough serum IgG level of more than 500 mg/dL was effective in preventing severe acute bacterial infections; however, pulmonary disease and sinusitis still occurred. The authors suggested that more intensive therapy to maintain a higher serum IgG level, for example, more than 800 mg/dL, may improve pulmonary outcome. The number of infections, days missed from school or work, and hospitalized days may not be sufficient indicators of adequate treatment. Therefore, the improvement or maintenance of pulmonary function is an important measure of the success of therapy. Generally, it should take about 3 to 6 months after beginning monthly IVIG infusions or a dosage change to reach equilibration (steady state). For persons who have a high catabolism of infused IgG, more frequent infusions—for instance, every 2 to 3 weeks—of smaller doses may maintain the serum level in the normal range. The rate of elimination of IgG may be higher during a period of active infection. Measuring serum IgG levels and adjusting to higher dosages or shorter intervals may be required.

The risk of adverse reactions during the initial treatment is relatively high. Adverse effects are generally associated with the presence of infections and formation of immune complexes. In patients with active infection, the dose should be halved, that is, 200 mg/kg, and the dose repeated 2 weeks later to achieve a full dose. Treatment should not be discontinued. After achieving normal serum IgG levels, adverse reactions are uncommon unless patients have active infections. The most common side effects include flushing, headache, nausea, vomiting, and myalgias that are often infusion rate-dependent. Severe anaphylactic episodes occur rarely in patients with IgE antibodies directed toward IgA.

Aseptic meningitis is a rare complication of IVIG, especially after large doses (1-2 g/kg), rapid infusions, and the treatment of patients with autoimmune disorders or inflammatory disease.⁴³ Pretreatment with aspirin (15 mg/kg/dose), acetaminophen (15 mg/kg/dose), diphenhydramine (1 mg/kg/dose), and/or hydrocortisone (6 mg/kg/dose, maximum 100 mg) 1 hour before the infu-

sion may prevent the adverse reactions.⁴⁴ Acute renal failure is a rare but significant complication of IVIG treatment, primarily in autoimmune patients receiving large doses of IVIG. IVIG containing sucrose as a stabilizer may confer greater risk for this renal failure. Risk factors for this adverse reaction include pre-existing renal insufficiency, diabetes mellitus, dehydration, age older than 65, sepsis, paraproteinemia, and concomitant use of nephrotoxic agents. Monitoring blood urea nitrogen and creatinine before starting the treatment and periodically thereafter are necessary.

One preparation was taken off the market after a series of cases of hepatitis C in 1994.⁴⁵ Routine screening for hepatitis C RNA by reverse transcriptase-polymerase chain reaction and the addition of a viral inactivation process in the final manufacturing step, for example, treatment with solvent/detergent, pasteurization, or both has significantly reduced the risk of transmission of hepatitis C and other viruses. There have been no reports of transmission of HIV or Creutzfeldt-Jakob disease in patients receiving IVIG replacement.

Immunomodulation. Since the first report by Imbach et al on the use of IVIG in childhood autoimmune thrombocytopenia purpura (AITP), IVIG has been used for the treatment of a variety of inflammatory and autoimmune disorders.⁴⁶ A number of mechanisms are postulated for the immunomodulatory effects of IVIG (Table IV).⁴⁷ The mechanism of action for IVIG proposed for increasing the platelet counts in ITP is by blockade of the Fc receptors on phagocytic cells in the reticuloendothelial systems of the spleen and liver. This Fc receptor blockade explains the rapid increase in platelet count after the administration of IVIG and leads to the prolonged survival of autoantibody-coated platelets. Support for this concept comes from the clinical studies of Debre et al, in which these investigators treated children with acute AITP with purified Fc γ fragments prepared from IVIG.⁴⁸

Takei and coworkers reported that IVIG contains antibodies to staphylococcal superantigen toxins that can block the T-cell stimulatory activities of these T-cell superantigens. IVIG contains antibodies to a broad range of staphylococcal and streptococcal enterotoxin.⁴⁹ It has been proposed that a mechanism of IVIG, at least in part, in Kawasaki disease is by neutralizing these bacterial superantigen enterotoxins, blocking vascular endothelial inflammation and damage.⁵⁰ IVIG has also been useful in toxic shock syndrome if used during the early phases of the disease. Studies in animals and human disease show that IVIG can inhibit complement uptake on target cells. IVIG inhibits the binding of activated fragments of C3 and C4 to target cells.⁵¹ Several reports by Dalakas and colleagues have shown that IVIG can reverse the complement-mediated endomysial capillary damage in patients with dermatomyositis.^{52,53} Abnormalities in the idiotype network have been postulated to be important in the pathophysiology of a number of autoimmune diseases. The presence of anti-idiotypic antibodies in IVIG was first suggested by the response to IVIG therapy of a patient with autoimmunity to factor VIII.^{54,55} Rossi and

Kazatchkine prepared F(ab) γ_2 fragments from commercial sources of IVIG that could neutralize or bind to known autoantibodies, such as anti-factor VIII, anti-thyroglobulin, anti-DNA, anti-intrinsic factor, and antineutrophil cytoplasmic antibodies (ANCA).⁵⁴ Several groups have reported that IVIG may be beneficial in the treatment of patients with ANCA-positive vasculitis who are refractory to conventional therapy.⁵⁶

Toxic epidermal necrolysis (TEN, or Lyell's syndrome) is a severe drug-induced bullous skin reaction. The mortality rate can be up to 30%. Separation of large areas of the skin at the dermo-epidermal junction by apoptosis of keratinocytes results in epidermal detachment and the appearance of scalded skin. Viard and colleagues reported that IVIG protected the keratinocytes from apoptosis by blocking the effects of Fas ligand (L) on the Fas receptor on keratinocytes. In an open, uncontrolled trial IVIG (0.2-0.75 g/kg/day for 4 consecutive days) was administered to 10 TEN patients. The skin progression was halted within 1 to 2 days, followed by rapid skin healing and a favorable outcome.⁵⁷ These immunomodulating effects of IVIG in patients with TEN represent another unique mechanism by which IVIG can modify the disease process. IVIG may be useful in other Fas-mediated inflammatory or autoimmune diseases.

IVIG has been shown to have a number of other immune-modulating effects. Sigman, et al reported that high concentrations of IVIG, in a dose-dependent manner, inhibited *in vitro* IgE production.⁵⁸ The inhibitory effect on IgE production was associated with a decrease in mRNA C γ transcripts. IVIG also inhibited B-cell proliferation. IVIG may regulate IgE synthesis through the Fc receptor on B cells. This suppressive activity was dependent on the Fc portion of IVIG in that the F(ab) γ_2 fragments of IgG had no effect. IVIG can suppress the synthesis of various cytokines from monocytes. The modulatory effects of IVIG on cytokine production may be mediated through the Fc γ receptor on mononuclear cells and T cells.

B cells and a subpopulation of T cells express a low affinity Fc γ receptor (Fc γ RIIB). This receptor subtype provides an inhibitory signal to cells through a pathway mediated by an immunoregulatory tyrosine-based inhibition motif (ITIM). Coligation of the B-cell receptor and Fc γ RIIB could be induced by the binding of IVIG through the Fc moiety of the IgG to the Fc γ RIIB receptor and the anti-idiotypic antibody specificity of the IgG molecule to the B-cell receptor.⁵⁹ Similar inhibitory Fc γ receptors are present on basophils and mast cells. Samuelsson et al investigated a murine model of immune thrombocytopenia. They found that the protective effects of IVIG required the inhibitory Fc receptor, Fc γ RIIB, as either disruption of the receptor or blocking with a monoclonal antibody reversed the therapeutic effects.⁵⁹ Thus, one mechanism by which IVIG may modulate B-cell immunoglobulin synthesis—and the immune effector responses of other cell types that have this Fc γ receptor, such as macrophages, mast cells, and others—is through the Fc γ RIIB receptor and its negative regulatory signal-

ing motifs. Probably no single mechanism accounts for the immunoregulatory activities of IVIG; the immunomodulating effects of IVIG are mediated by multiple effects on various pathways of inflammatory and immune effector responses.

Polyclonal antibodies directed against cells

Rh (D) immune globulin is a human IgG globulin solution containing an enriched fraction of antibodies against the D blood group antigen (Table III). When given to the Rh-negative mother within 72 hours of the birth of an Rh-positive baby, the maternal antibody response to the Rh-positive cells from the fetus, which cross the placenta, can be suppressed. This represents one of the most effective and specific immunosuppressive therapies available today and has prevented thousands of cases of erythroblastosis fetalis, or hemolytic disease, of the newborn.⁶⁰ The rationale for immunosuppression in this setting is based on the fact that the primary antibody response to the foreign D antigen is blocked by specific anti-D antibody administered passively at the time of exposure.

Antithymocyte globulin is a purified immunoglobulin prepared from hyperimmune serum of horse, rabbit, sheep, or goat after immunization with human thymic lymphocytes (Table III). Intravenous administration results in binding to the surface of circulating T lymphocytes, resulting in lymphopenia and profound suppression of cellular immune responses. The half-life is between 3 and 9 days. Major toxicities include serum sickness and nephritis. It is used for the treatment of idiopathic aplastic anemia and acute rejection of solid organ renal and cardiac transplants.⁶¹

Hyperimmune globulins (polyclonal and monoclonal) for infectious diseases

Specific immune globulins, also called "hyperimmune globulins," are prepared from select donors who have high titers of the desired antibody, either naturally acquired or stimulated through immunization. Samples of specific immune globulins for use in the passive protection of infectious diseases include hepatitis B immune globulin, rabies immune globulin, tetanus immune globulin, varicella-zoster immune globulin, cytomegalovirus immunoglobulin intravenous, and respiratory syncytial virus immune globulin intravenous.

Varicella-zoster virus (VZV) polyclonal. Varicella-zoster immune globulin (VZIG) is used to prevent or modify the course of varicella, but is not effective once the disease is established.⁶² VZIG should be administered as soon as possible, and no later than 96 hours after exposure (Table III). Provided significant exposure has occurred, potential candidates for VZIG include immunocompromised children without a history of chickenpox, susceptible pregnant women, newborn infants whose mother had onset of chickenpox within 5 days before delivery or 48 hours after delivery, hospitalized premature infants (≥ 28 weeks' gestation) whose mother has no history of chickenpox and is seronegative,

and the hospitalized preterm infants (< 28 weeks' gestation or ≤ 1000 g), regardless of maternal history. VZIG can be obtained through the local American Red Cross Blood Services. Immunocompromised children with no history of varicella, regardless of serologic results, probably should be given VZIG. Patients with primary immune deficiency diseases receiving monthly high-dose IVIG are likely to be protected and probably do not require VZIG. VZIG is given by intramuscular injection. One vial containing 125 U is given for each kg of body weight. The suggested maximum dose is 625 U.

Respiratory syncytial virus-specific antibodies. Respiratory syncytial virus (RSV) is a leading cause of lower respiratory illness in children. It is an important pathogen in immunocompromised individuals, especially premature infants, and children with chronic lung disease, congenital heart disease, multiple congenital anomalies, and certain immunodeficiencies (Table III). Two approaches are available to prevent RSV infection in these at-risk children: respiratory syncytial virus immune globulin intravenous (RSV-IGIV), which is prepared from donors selected for high serum titers of RSV neutralizing antibody, and palivizumab, a humanized mouse-monoclonal antibody that is given intramuscularly.⁶³ Both agents are approved for the prevention of RSV in children younger than 24 months of age with bronchopulmonary dysplasia or with a history of premature birth (< 35 weeks' gestation). RSV-IGIV is given monthly throughout the RSV season at a dose of 15 mL/kg (750 mg/kg). Palivizumab is administered intramuscularly in a dose of 15 mg/kg once a month during the RSV season. Palivizumab is preferred for most high-risk children because of its ease of administration, safety, and effectiveness. Patients with severe chronic lung disease may benefit from RSV prophylaxis for two seasons, especially those who have ongoing medical problems. RSV-IGIV is contraindicated in children with cyanotic heart disease. In contrast, palivizumab is pending approval before the Food and Drug Administration for the use in children with cyanotic congenital heart disease.

Monoclonal antibodies as immunomodulators

Muromonab-CD3 is a murine monoclonal antibody to the CD3 antigen of human T cells (Table III). It is a biologically purified IgG2a immunoglobulin that is directed against a glycoprotein on the surface of human T-cell marker CD3, which is associated in vitro with the antigen recognition structure of T cells that is essential for signal transduction. In vivo, there is a rapid decrease in circulating CD3⁺CD8⁺ and CD3⁺CD4⁺ cells, which are undetectable in the peripheral blood from 2 and 7 days after infusion. Patients develop neutralizing antibodies with repeated treatment that abrogates some of this activity. Muromonab-CD3 is approved for the treatment of acute allograft rejection in renal transplant recipients and for GCS-resistant acute allograft rejection of heart and liver transplants.⁶⁴ Most patients experience acute clinical syndrome (cytokine release syndrome) associated with

the initial dose of muromonab-CD3; manifestations range from a flu-like illness to capillary leak, hypotension, and multiorgan failure.

Infliximab is an IgG1k monoclonal antibody that is chimeric (human constant and murine variable regions). It binds specifically and with high affinity to TNF- α (Table III). TNF- α induces IL-1 and IL-6, promotes leukocyte migration, activates neutrophils and eosinophils, and induces acute phase reactant production and tissue degrading enzymes.⁶⁵ Infliximab is an important addition to the therapeutic treatments of patients with rheumatoid arthritis and is used in conjunction with methotrexate. It is also indicated for patients with Crohn's disease who experience an inadequate response to conventional therapy. Side effects include autoantibody production and a lupuslike syndrome, acute infusion reactions, infections, and possible increased incidence of malignancy.

Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody (Campeth-1H) that is directed against the 21-28 Kd cell surface protein, which is expressed on the surface of normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages, and tissues of the male reproductive system (Table III).⁶⁶ CD52 is not present on erythrocytes or hematopoietic stem cells. Alemtuzumab is indicated for the treatment of B-cell chronic lymphocytic leukemia in patients who have been treated with alkylating agents and who have failed fludarabine therapy.⁶⁷ The broad array of immune cells that carry the CD52 receptor predict that the immunosuppressive properties in patients are more profound than that seen with monoclonal directed at more "selective" receptors. Alemtuzumab produces a profound lymphopenia that is associated with the development of opportunistic infections. Anti-infective prophylaxis is recommended upon initiation of therapy and for a minimum of 2 months after the last dose or until absolute CD4⁺ cell numbers are higher than 200 cells/mm³. The median time to recovery to greater than 200 cells/mm³ is 2 months; however, the baseline CD4⁺ cell number may not be reached for 12 months. Life-threatening bone marrow aplasia has also occurred in some patients treated with recommended dosages. Clinical trials are ongoing, using this antibody as GVHD prophylaxis and as a conditioning therapy prior to nonablative HCT.

Rituximab is a chimeric human/murine monoclonal antibody against the cell surface antigen CD20 of normal and malignant B lymphocytes (Table III). Intravenous administration of rituximab in humans results in a disappearance of B cells from the circulation for weeks to months, depending on the dosing schedule. CD20 is expressed on more than 90% of non-Hodgkin's lymphomas and mature normal B cells but not hematopoietic cells, pro-B cells, normal plasma cells, or other normal tissues. It is approved for the treatment of patients with relapsed or refractory, low-grade, or follicular CD20-positive, B-cell non-Hodgkin's lymphoma.⁶⁸ It is also being evaluated for the treatment of several autoimmune conditions.

An alternative monoclonal anti-CD20, ibritumomab, has been linked to the isotope yttrium-90 using tiuxetan (a linker chelator) to create a radioimmunotherapy agent.⁶⁹ Ibritumomab tiuxetan, the first radioimmunotherapy to gain FDA sanction (February 2002), is useful for the treatment of patients with relapsing or refractory low-grade, follicular, or transformed B-cell non-Hodgkin's lymphoma. The addition of a radionuclide appears to boost the antibody therapy response rate by combining the specificity of the antibody with the cytotoxic impact of molecular radiotherapy, when used in a dosing schedule that includes unlabeled rituximab and follows a two-stage approach. Eighty percent of patients responded in a multicenter study (30% achieved a complete response), leading to fast-track approval using this approach.⁷⁰ Other monoclonal antibodies are seeing their way into the clinic, including humanized anti-CD25, which is used to treat certain selected T-cell malignancies and post-solid organ transplant rejection, and is being evaluated in certain autoimmune diseases.

Omalizumab is a humanized murine monoclonal antibody (rhuMAb-E25) specific for the Fc-binding domain of IgE (Table III). This anti-IgE monoclonal antibody has been tested in allergic asthmatic subjects and was shown to suppress both early- and late-phase responses to inhaled allergen.⁷¹ When omalizumab was tested against placebo in a 20-week trial of steroid-dependent allergic asthmatic subjects, asthma and steroid-use scores decreased significantly.⁷² This and other anti-IgE monoclonal antibodies being proposed for human use may prove useful in moderate to severe asthma. A note of caution was sounded by the observation that inhaled anti-IgE generated IgG anti-rhuMAb-E25 antibodies.⁷³ The mechanism of action of rhuMAb-E25 is thought to be the competition of the molecule for free IgE's Fc region, thus preventing the free IgE from binding to the mast cell surface IgE receptor through its Fc region.

CYTOKINE RECEPTOR INHIBITORS

Soluble TNF receptor

TNF is an important proinflammatory cytokine that plays a role in the pathogenesis of rheumatoid arthritis. Immune-modifying agents, which inhibit the activity of TNF, are available for the treatment of several inflammatory diseases including rheumatoid arthritis (Table III). Etanercept (Enbrel) is a genetically engineered fusion protein consisting of two identical chains of recombinant human TNF-receptor p75 monomer fused with the Fc domain of human IgG₁.⁷⁴ This soluble fusion protein binds and inactivates TNF, thereby competing with cell-bound TNF-receptors for free TNF. Several randomized, double-blind, placebo-controlled trials have shown that Etanercept treatment can lead to significant clinical benefit with minimal toxicity in patients with rheumatoid arthritis who have had an inadequate response to other disease-modifying drugs. A trial in adults of the addition of methotrexate to Etanercept therapy resulted in rapid and sustained improvement in rheumatoid arthritis

patients. The patients received 25 mg of Etanercept subcutaneously twice weekly. The only adverse events associated with Etanercept treatment were mild redness at the injection site. Some patients experience bone marrow suppression; careful monitoring is advisable.

Soluble IL-1 receptor

IL-1 is a proinflammatory cytokine that is induced in response to inflammatory stimuli and mediates various physiologic responses including inflammation and immunologic responses (Table III). It has a broad range of biological activities, including cartilage degradation caused by its induction in the rapid loss of proteoglycans and stimulation of bone reabsorption. Anakinra is a recombinant, nonglycosylated form of the human IL-1 receptor antagonist (IL1Ra).⁷⁵ Anakinra blocks the biological activity of IL-1 by competitively inhibiting IL-1 binding to the IL-1 type 1 receptor that is expressed in a wide variety of tissues and organs. Anakinra has been evaluated in three randomized double-blind, placebo-controlled trials of patients with active rheumatoid arthritis. Anakinra can either be used alone as monotherapy or, more commonly, in combination with a disease-modifying antirheumatic drug, such as methotrexate. The recommended dose for the treatment of patients with rheumatoid arthritis is 100 mg/day administered daily by subcutaneous injection. The most common adverse reaction is reactions at the injection site. Other adverse events occurred at the same frequency as the control group treated with placebo.

IL-2 receptor inhibitors

Denileukin diftitox is a recombinant DNA-derived cytotoxic protein composed of the amino acid sequences for diphtheria toxin fragments A and B, followed by the sequences for IL-2 receptor. It is available for clinical use but as yet has no specific indications for use in humans.

Plasmapheresis

Plasmapheresis is a particular apheresis method that removes plasma proteins, including immunoglobulin and immune complexes, from the intravascular circulation. IgM and IgG are effectively reduced, and the procedure is clinically useful for the emergent treatment of thrombotic thrombocytopenic purpura, myasthenia gravis, Goodpasture's syndrome, and hyperviscosity secondary to Waldenström's macroglobulinemia. The fact that plasmapheresis has not been more universally effective for the treatment of immune complex diseases, such as lupus erythematosus and cryoglobulinemia, is at least partially related to the ongoing or increased pathogenic antibody production that occurs after treatments. Plasmapheresis for chronic conditions is usually combined with immunosuppressive therapy (ie, cyclophosphamide and/or glucocorticoids), which may be administered before or after the plasmapheresis treatments that are usually given as a series over 12 weeks. Semi-selective plasmapheresis uses affinity separation methods that allow specific blood components

to be removed. *Staphylococcus aureus* Cowan strain I-derived protein A columns bind the Fc portion of IgG and is used for the treatment of idiopathic thrombocytopenic purpura.

SUMMARY

The clinical immunologist, while still relying predominantly on pharmacologic means of immunosuppression, now has the reagents long dreamed of to afford more selective and specific means of immunosuppression, immunomodulation, and immunotherapy. The techniques of recombinant DNA technology and molecular biology have produced monoclonal antibodies and receptor antagonists that are effectively changing the practice of clinical immunology. Application of this new science to such common diseases as allergic asthma offers the possibility of changing the natural history of allergic and immunologic diseases.

REFERENCES

- Anderson RE, Warner NL. Ionizing radiation and the immune response. *Adv Immunol* 1976;24:215-335.
- Fletcher GH. Clinical dose-response curves of human malignant epithelial tumors. *Br J Radiol* 1973;46:1-12.
- Present DH, Korelitz BJ, Wisch H, Glass JL, Sachar DB, Paternack BS. Treatment of Crohn's disease with 6-mercaptopurine. *N Engl J Med* 1980;302:981-86.
- Sullivan KM, Mori M, Sanders J, Siadak M, Witherspoon RP, Anasetti C, et al. Late complications of allogeneic and autologous marrow transplantation. *Bone Marrow Transplant* 1992;10:127-34.
- Johnson WJ, Dimartino MJ, Melnier PC, Muirhead KA, Hanna N. Methotrexate inhibits macrophage activation as well as vascular and cellular inflammatory events in rat adjuvant induced arthritis. *J Rheumatol* 1988;15:745-9.
- Roenigk HH Jr, Auerbach R, Maibach HI, Weinstein GD. Methotrexate in psoriasis: revised guidelines. *J Am Acad Dermatol* 1988;19:145.
- Mullarkey M. Immunosuppressive therapy for asthma. *Allergy Proceedings* Mar-Apr. 1995;16:81-4.
- Stewart GE II, Diaz JD, Lockey RF, Seleznick MJ, Trudeau WL, Ledford DK. Comparison of oral pulse methotrexate with placebo in the treatment of severe glucocorticosteroid-dependent asthma. *J Allergy Clin Immunol* 1994;94:482-9.
- Giannini EH, Brewer EJ, Kuzmina N, Shaikov A, Maximov A, Vorontsov I, et al. Methotrexate in resistant juvenile rheumatoid arthritis. Results of the U.S.A.-U.S.S.R. double blind, placebo-controlled trial. *N Engl J Med* 1992;326:1043-9.
- Dahl MGC, Gregory MM, Schener PJ. Liver damage due to methotrexate in patients with psoriasis. *Br Med J* 1971;1:625-30.
- Boumpas DT, Fessler BJ, Austin HA 3rd, Ballow JE, Klippel JH, Lockshin MD. Systemic lupus erythematosus: emerging concepts. I: renal, neuropsychiatric, cardiovascular, pulmonary, and hematologic disease. *Ann Intern Med* 1995;122:940.
- Fauci AS, Haynes BF, Katz P, Wolff SM. Wegener's granulomatosis: prospective clinical and therapeutic experience with 85 patients for 21 years. *Ann Intern Med* 1983;98:76.
- Morris RE. New small molecule immunosuppressants for transplantation: review of essential concepts. *J Heart Lung Transplant* 1993;12:S275.
- Ensley RD, Bristow MR, Olsen SL, Taylor DO, Hammond EH, O'Connell JB, et al. The use of mycophenolate mofetil (RS-61443) in human heart transplant recipients. *Transplantation* 1993;56:75-82.
- Moser MA. Options for induction immunosuppression in liver transplant recipients. *Drugs* 2002;62:995-1011.
- Beato M. Gene regulation by steroid hormones. *Cell* 1989;3:335-45.
- Burnstein KL, Cidlowski JA. Regulation of gene expression by glucocorticoids. *Annu Rev Physiol* 1989;51:683.

18. Scheinman RI, Cogswell PC, Lofquist AK, Baldwin AS Jr. Role of transcriptional activation of I kappa B alpha in mediation of immunosuppression by glucocorticoids. *Science* 1995;270:283-6.
19. Radomski MW, Palmer RM, Moncada S. Glucocorticoids inhibit the expression of an inducible, but not the constitutive, nitric oxide synthase in vascular endothelial cell. *Proc Natl Acad Sci* 1990;87:10043-7.
20. Evans RM. The steroid and thyroid hormone receptor superfamily. *Science* 1988;240:889.
21. Nelson RP, Lockett RF. Treatment of asthma with glucocorticosteroids. *South Med J* 1988;81:761-9.
22. Mattila PS. The actions of cyclosporine A and FK 506 on T-lymphocyte activation. *Biochem Soc Trans* 1996;24:45-9.
23. Muraoka K, Fujimoto K, Sun X, Yoshioka K, Shimizu K, Yagi M, et al. Immunosuppressant FK506 induces interleukin-6 production through the activation of transcription factor nuclear factor (NL)-kappa B. *J Clin Invest* 1996;97:2433-9.
24. Faulds D, Goa KL, Benfield P. Cyclosporin. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in immunoregulatory disorders. *Drugs* 1993;45:953-1040.
25. Masuda K, Nakajima A, Urayama A, Nakae K, Kogure M, Inaba G. Double-masked trial of cyclosporine versus colchicines and long-term open study of cyclosporine in Behcet's disease. *Lancet* 1989;1:1093-96.
26. Cockfield SM, Preiksaitis JK, Jewell LD, Parfrey NA. Post-transplant lymphoproliferative disorder in renal allograft recipients, clinical experience and risk factor analysis in single center. *Transplantation* 1993;56:88-93.
27. Brazelton TR, Morris RE. Molecular mechanisms of action of new xenobiotic immunosuppressive drugs: tacrolimus (FK506), sirolimus (rapamycin), mycophenolate mofetil and leflunomide. *Curr Opin Immunol* 1996;8:710-20.
28. Eschbach JW, Egrie JC, Downing MR, Browne JK, Adamson JW. Correction of the anemia of progressive renal failure with recombinant human erythropoietin. *N Engl J Med* 1989;321:158-63.
29. Fischl M, Galpin JE, Levine JD, JE, Henry DH, Kennedy P, et al. Recombinant human erythropoietin therapy for AIDS patients treated with AZT: a double-blind, placebo-controlled clinical study. *N Engl J Med* 1990;322:1488-93.
30. Brandt SJ, Peters WP, Atwater SK, Kurtzberg J, Borowitz MJ, Jones RB, et al. Effect of recombinant human granulocyte-macrophage colony-stimulating factor on hematopoietic reconstitution after high-dose chemotherapy and autologous bone marrow transplantation. *N Engl J Med* 1988;318:869-76.
31. Hammond WP IV, Price TH, Souza LM, Dale DC. Treatment of cyclic neutropenia with granulocyte colony-stimulating factor. *N Engl J Med* 1989;320:1306-11.
32. Balkwill FR. Interferons. *Lancet* 1989;1:1060-3.
33. Kimchi A. Autocrine interferon and the suppression of the c-myc nuclear oncogene. *Interferon* 1987;8:86-110.
34. Dorr RT. Interferon-alpha in malignant and viral diseases. *Drugs* 1993;45:1977-211.
35. Morgan DA, Ruscetti FW, Gallo R. Selective in vitro growth of T lymphocytes from normal human bone marrows. *Science* 1976;193:1007-8.
36. Bindon C, Czerniecki M, Ruell P, Edwards A, McCarthy WH, Harris R, et al. Clearance rates and systemic effects of intravenously administered interleukin-2 (IL-2) containing preparations in human subjects. *Br J Cancer* 1983;47:123-33.
37. Schwartzentruber DJ. Biologic therapy with interleukin-2: clinical applications. In: DeVita VT Jr, Hellman S, Rosenberg SA, editors. *Biologic therapy of cancer*. 2nd ed. Philadelphia: JB Lippincott; 1995. p. 235-49.
38. Dutcher JP, Logan T, Gordon M, Sosman J, Weiss G, Margolin K, et al. Phase II trial of interleukin 2, interferon alpha and 5-fluoruracil in metastatic renal cell cancer: a cytokine working group study. *Clin Cancer Res* 2000;6:3442-50.
39. Fisher RI, Rosenberg SA, Fyfe G. Long-term survival update for high-dose recombinant interleukin-2 in patients with renal cell carcinoma. *Cancer J Sci Am* 2000;6 Suppl 1:S55-7.
40. Burks AW, Sampson HA, Buckley RH. Anaphylactic reactions after gamma globulin administration in patients with hypogammaglobulinemia: deflection of IgE antibodies to IgA. *N Engl J Med* 1986;314:560.
41. Roifman CM, Levison H, Gelfand EW. High-dose versus low-dose intravenous immunoglobulin in hypogammaglobulinemia and chronic lung disease. *Lancet* 1987;i:1075-7.
42. Quartier P, Debre M, De Blic J, de Sauverzac R, Sayegh N, Jabado N, et al. Early and prolonged intravenous immunoglobulin replacement therapy in childhood agammaglobulinemia: a retrospective survey of 31 patients. *J Pediatr* 1999;134:589-97.
43. Kressebuech H, Schaad UB, Hirt A, Bianchetti MG. Cerebrospinal fluid inflammation induced by intravenous immunoglobulin. *Pediatr Infect Dis J* 1992;11:894-6.
44. Lederman HM, Roifman CM, Lavi S, Gelfand EW. Corticosteroids for prevention of adverse reactions to intravenous immune serum globulin infusions in hypogammaglobulinemic patients. *Am J Med* 1986;81:443-6.
45. Anonymous. Outbreak of hepatitis C associated with intravenous immunoglobulin administration—United States, October 1993-June 1994. *MMWR* 1994;43:505-9.
46. Imbach P, Barandun S, d'Apuzzo V, Baumgartner C, Hirt A, Morell A, et al. High dose intravenous gamma globulin for idiopathic thrombocytopenic purpura in childhood. *Lancet* 1981;1:1228-31.
47. Ballow M. Mechanisms of action of intravenous immune serum globulin in autoimmune and inflammatory diseases. *J Allergy Clin Immunol* 1997;100:151-7.
48. Debre M, Bonnet MC, Fridman WH, Carosella E, Philippe N, Reinert P, et al. Infusion of Fc gamma fragments for treatment of children with acute immune thrombocytopenic purpura. *Lancet* 1993;342:945-9.
49. Takei S, Arora YK, Walker SM. Intravenous immunoglobulin contains specific antibodies inhibitory to activation of T cells by staphylococcal toxin superantigens. *J Clin Invest* 1993;91:602-7.
50. Leung DY. Kawasaki syndrome: immunomodulatory benefit and potential toxin neutralization by intravenous immune globulin. *Clin Exp Immunol* 1996;104(suppl):1:49.
51. Basta M, Fries LF, Frank MM. High doses of intravenous Ig inhibit in-vitro uptake of C4 fragments onto sensitized erythrocytes. *Blood* 1991;77:376-80.
52. Basta M, Dalakas MC. High-dose intravenous immunoglobulin exerts its beneficial effect in patients with dermatomyositis by blocking endomysial deposition of activated complement fragments. *J Clin Invest* 1991;94:1729-35.
53. Dalakas MC, Illa I, Dambrosia JM, Soueidan SA, Stein DP, Otero C, et al. Controlled trial of high-dose immune globulin infusions as treatment for dermatomyositis. *N Engl J Med* 1993;329:1993-2000.
54. Rossi F, Kazatchkine MD. Antidiotypes against autoantibodies in pooled normal human polyspecific IgG. *J Immunol* 1989;143:4104-9.
55. Sultan Y, Rossi F, Kazatchkine MD. Recovery from anti-VIIIc (anti-hemophilic factor) autoimmune disease is dependent on generation of anti-idiotypes against anti VIIIc autoantibodies. *Proc Natl Acad Sci USA* 1987;84:828-31.
56. Jayne DRW, Esnault VLM, Lockwood CM. Anti-idiotype antibodies to anti-myeloperoxidase autoantibodies in patients with systemic vasculitis. *J Autoimmunity* 1993;6:221-6.
57. Viard I, Wehrli P, Bullani R, Schneider P, Holler N, Salomon D, et al. Inhibition of toxic epidermal necrolysis by blockade of CD95 with human intravenous immunoglobulin. *Science* 1998;282:490-3.
58. Sigman K, Ghibu W, Sommerville B, Toledano BJ, Bastein Y, Cameron L, et al. Intravenous immunoglobulin inhibits IgE production in human B lymphocytes. *J Allergy Clin Immunol* 1998;102:421-7.
59. Samuelsson A, Towers TL, Ravetch JV. Anti-inflammatory activity of IVIG mediated through the inhibitory Fc receptor. *Science* 2001;291:484-6.
60. Contreras M, de Silva M. The prevention and management of haemolytic disease of the newborn. *J R Soc Med* 1994;87:256-8.
61. Schwinghammer TL, Bloom EJ. Pharmacologic prophylaxis of acute graft-versus-host disease after allogeneic marrow transplantation. *Clin Pharm* 1993;12:736-61.
62. Centers for Disease Control and Prevention. Prevention of varicella: recommendations of the Advisory Committee on Immunization Practices. *MMWR* 1996;45:1-36.
63. American Academy of Pediatrics, Committee on Infectious Diseases and Committee on Fetus and Newborn. The prevention of respiratory syncytial virus infections: indications for the use of palivizumab: an update on the use of RSV-IVIG. *Pediatrics* 1998;102:1211-6.
64. Waid TH, Lucas BA, Thompson JS, Brown SA, Munch L, Prebeck RJ, et al. Treatment of acute cellular rejection with T10B9.1A-31 or OKT3 in renal allograft recipients. *Transplantation* 1992;53:80-6.
65. Targan SR, Hanauer SB, van Deventer SJ, Mayer L, Present DH, Braakman T, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's diseases. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997;337:1029-35.

66. Waldmann H. A personal history of the CAMPATH-1H antibody. *Med Oncol* 2002;19(suppl):S3-9.
67. Rai KR, Freter CE, Mercier RJ, Cooper MR, Mitchell BS, Stadtmauer EA, et al. Alemtuzumab in previously treated chronic lymphocytic leukemia patients who also had received fludarabine. *J Clin Oncol* 2002;20:3891-7.
68. Wiseman GA, White CA, Witzig TE, Gordon LI, Emmanouilides C, Raubitschek A, et al. Radioimmunotherapy of relapsed non-Hodgkin's lymphoma with zevalin, a 90Y-labeled anti-CD20 monoclonal antibody. *Clin Cancer Res* 1999;5(suppl):3281s-6s.
69. Anti-CD20 mAbs: modifying therapeutic strategies and outcomes in the treatment of lymphoma patients. *Expert Rev Anticancer Ther* 2002;2:323-9.
70. Witzig TE, Flinn IW, Gordon LI, Emmanouilides C, Czuczman MS, Saleh MN, et al. Treatment with ibritumomab tiuxetan radiotherapy in patients with rituximab-refractory follicular non-Hodgkin's lymphoma. *J Clin Oncol* 2002;20:3262-9.
71. Boulet LP, Chapman KR, Cote J, Kalra S, Bhagat R, Swystun VA, et al. Inhibitory effects of an anti-IgE antibody E25 on allergen-induced early asthmatic response. *Am J Respir Crit Care Med* 1997;155:1835-40.
72. Milgrom H, Fick RB Jr, Su JQ, Reimann JD, Bush RK, Watrous ML, et al. Treatment of allergic asthma with monoclonal anti-IgE antibody. rhuMAb-E25 Study Group. *N Engl J Med* 1999;341:1966-73.
73. Fahy JV, Fleming HE, Wong HH, Liu JT, Su JQ, Reimann J, et al. The effect of an anti-IgE monoclonal antibody on the early- and late-phase responses to allergen inhalation in asthmatic subjects. *Am J Respir Crit Care Med* 1997;155:1828-34.
74. Weinblatt ME, Kremer JM, Bankhurst AD, Bulpitt KJ, Fleischmann RM, Fox RI, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340:253-9.
75. Bresnihan B, Alvaro-Gracia JM, Cobby M, Doherty M, Domljan Z, Emery P, et al. Treatment of rheumatoid arthritis with recombinant human interleukin-1 receptor antagonist. *Arthritis Rheum* 1998;41:2196-204.