The Art and Science of Infusion Nursing

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Emerging Therapies for Autoimmune Disorders

ABSTRACT

Several monoclonal antibodies and other biologic drugs are used to treat a variety of common autoimmune disorders that are progressive in nature or resistant to standard therapies. Although monoclonal antibodies were recently removed from the hazardous drugs list, most of these drugs are considered high-risk substances that require specialized knowledge regarding care before, during, and after administration. Yet no national standards exist for nurses working with autoimmune patients, nor have minimum nursing practice competency guidelines been identified. Expert practitioners must continue to educate other health care professionals about the drugs,their intended and off-label uses, their potential side effects, and proactive measures that need to be taken to ensure patient safety during the entire drug administration process.

Key words: autoimmune disorders, autoimmune theories, biologic drugs, immune system, emerging therapies, hypersensitivity reactions, monoclonal antibodies, nursing administration, nursing interventions, side effects

Numerous monoclonal antibodies (MAbs) initially used to treat malignancies have been developed, researched, and incorporated into the treatment plans for several autoimmune disorders with great success when compared with traditional therapies. Some agents have become the new standard of care for many of these incurable diseases.

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As a result of recent clinical success, combined with the potential for substantial financial profits from drug patent rights, specific Food and Drug Administration (FDA) approvals, and difficulty in replicating and manufacturing these biologic substances, pharmaceutical companies are investing vast resources in the development of MAb drug therapy. They are filling the FDA's approval pipeline with drug therapies, while they and other researchers progress through phase clinical trials with the hope of finding unique niche treatments that will significantly benefit patients who suffer from common autoimmune disorders.

This article will review the immune system and autoimmune pathophysiology, highlight emerging MAb therapies prescribed for common autoimmune disorders, and describe each agent in detail to benefit a nurse's perspective. All the drugs discussed in this article, with the exception of abatacept, carry a black-box warning.

AUTOIMMUNE STATISTICS

Approximately 150 chronic conditions are considered autoimmune disorders. Together they constitute the third most-common illness diagnosed in Americans,[1] affecting some 23.5 million people in the United States.[2] About 75% to 85% of cases occur in women in their childbearing years.[1] Autoimmune diseases are the leading cause of death in female children and in women in all age groups up to age 65.[2] The National Institutes of Health has estimated the direct health care costs of autoimmune diseases to be more than $100 billion a year.[2]

AUTOIMMUNE DISORDERS

Autoimmune diseases can be categorized according to the organ system they affect most. The nervous, gastrointestinal, integumentary, endocrine, and musculoskeletal systems, as well as blood and blood vessels, are often affected by autoimmune processes.[3]

Autoimmune nervous system disorders, for example, include multiple sclerosis (MS), myasthenia gravis, and Guillain-Barré syndrome. Autoimmune gastrointestinal

disorders include celiac disease, Crohn's disease (CD), ulcerative colitis (UC), and autoimmune hepatitis, while autoimmune blood and blood vessel disorders include systemic lupus erythematosus (SLE), antiphospholipid antibody syndrome, vasculitis, autoimmune hemolytic anemia, and idiopathic thrombocytopenia purpura. Autoimmune integumentary disorders include scleroderma, psoriasis, Sjögren's syndrome, dermatomyositis, epidermolysis bullosa, bullous pemphigoid, vitiligo, and chronic urticaria. Autoimmune endrocrine disorders include type I diabetes mellitus, Graves' disease, Hashimoto's thyroiditis, Addison's disease, and autoimmune orchitis and oophoritis. Finally, autoimmune musculoskeletal disorders include rheumatoid arthritis (RA), ankylosing spondylitis (AS), and systemic juvenile idiopathic arthritis (SJIA).

IMMUNE SYSTEM

The immune system works to protect the individual by identifying and eliminating foreign, potentially pathogenic substances from inside the body. This is accomplished by a complex network of general and specialized cells that recognize foreign antigens by comparing them with self-antigens.

Lymphocytes are white blood cells that fight infections. They include T and B cells, as well as natural killer (NK) cells. T cells form the cell-mediated or specific immune response. They include helper T cells (CD4); cytotoxic killer T cells (CD8); central and effector memory T cells (CD4 and CD8); regulatory T cells; natural killer T cells (which are unique from NK cells); and mucosal-associated invariant or gamma delta T cells, which are found in the gut mucosa.

B cells are the other component of the adaptive immune response, known as humoral immunity, and are responsible for antibody production against specific antigens. B cells include plasma B cells, which are antibody factories; memory B cells, which live for a long time and are responsible for the faster secondary immune response to a known pathogen; B1 cells, which primarily express immunoglobulin (Ig) M rather than IgG and are found in the peritoneal and pleural cavities; marginal-zone, noncirculating B cells found in the spleen; and follicular B cells, which reside in lymphoid organs, such as the spleen and lymph nodes.

NK cells are nonspecific in nature, but defend the host from tumors and virus-infected cells by recognizing subtle differences in major histocompatibility complex (MHC) class I molecules.

Other nonspecific white blood cells include neutrophils, granulocytes responsible for defending against bacterial or fungal infections through phagocytosis; monocytes, longer-lived phagocytic and antigen-presenting cells, or APCs, in the bloodstream, which are able to replace their lysosomal contents; macrophages, monocytes that differentiate and are capable of moving from the bloodstream into body tissues to phagocytize foreign substances; and mast cells, resident granulocyte cells located inside certain tissue with a high concentration of histamine and heparin.

Dendritic cells are also resident immune cells in tissues that are exposed to the external environment, such as the skin and linings of the nose, lungs, stomach, and intestines. They function as APCs, or messengers, between the innate and adaptive immune systems and should not be confused with the dendrites of neurons.

Finally, several proinflammatory cytokines—such as histamines, interleukins (ILs), interferons, leukotrienes, prostoglandins, and tumor necrosis factor alpha (TNF-α)—are produced by many immune cells that promote systemic inflammation through a variety of chemical messengers between APCs and T and B cells.[4-8]

MAJOR HISTOCOMPATIBILITY COMPLEX

Self-antigens are determined by the MHC genes located on the short arm of chromosome 6.[9] Three classes of MHC genes (I, II, and III) are physically and genotypically present there. However, mutations in class II genes (DR, DQ, and DP) have been implicated most often as the etiological source in the development of most autoimmune disorders.[10] MHC class II mutations—such as DR 2, DR 3, and DR 4, as well as TNF—have been identified as a common denominator in 3 of the 6 most prevalent autoimmune diseases.[10]

THEORIES OF AUTOIMMUNE PATHOGENESIS

Several theories of the development of autoimmune disorders have been postulated. The genetic predisposition of mutations in the MHC class II genes has been supported by recent evidence. Exposures to harmful environmental substances with ill effects to the immune system have been considered, as has exposure to certain infections—in particular viral infections—in the pathogenesis of type I diabetes mellitus. In this theory, cells infected with a simple cold virus initiate an immune response in which immune cells mistakenly confuse viral-infected cells with healthy pancreatic beta cells, leading to destruction and an unintended permanent autoimmune process. Hormonal imbalances, such as with pregnancy or estrogen metabolites, have also been implicated. However, the consensus is that estrogen imbalances are not necessarily causative. Instead, they coexist in many autoimmune states. A final theory, described as microchimerism, has gained support recently. Microchimerism is the 2-way trafficking of immune cells between the mother and fetus through the placenta.[11] Exchanged cells can form long-lasting cell lines in each distinct, nonidentical individual; these cell lines are

immunologically active and measurable even decades later. This theory suggests a temporary tolerance between self- and nonself antigens during pregnancy to prevent an immune response against the fetus. Research supports increased autoimmune activity in mothers for several years after giving birth, a response that has been found to be even greater with male children.[12]

MONOCLONAL ANTIBODIES

Discovered less than 30 years ago, MAbs have become the magic bullet for targeted therapies against cancer and are now used to successfully treat, although not cure, autoimmune diseases.

The structure of MAbs mimics the structure of typical antibodies produced by B cells. Antibodies have 2 unique fragment (F) components: an Fc (crystallizable) region, and the Fab (antigen-binding) region.[13] The Fc region is composed of 2 or 3 constant domains that code for specific binding sites to other immune molecules, such as complement proteins, T and B cells, and macrophages that lead to recognition, lysis, and degranulation of mast cells, basophils, and eosinophils. The Fab region is made up of 1 constant and 1 variable domain (Fv), which target unique receptors, allowing for specific antigen binding (antigenic determinant, or epitope, the site on an antigen at which a specific antibody becomes attached).

The earliest MAbs were fully murine—that is, an entire rodent MAb specifically derived from a transgenic mouse. These were followed by the development of chimeric MAbs, which are MAbs composed of a mix of 2 different species—part human and part mouse. Several chimeric MAbs continue to have clinical uses. Because of potentially serious hypersensitivity and anaphylactic reactions—known as serum sickness—caused by the different species' cell surface antigens, newer, more preferred agents, such as humanized (possessing a slight mixture of human and nonhuman Fab regions) and human (strictly human Fab regions) MAbs, are being actively developed and prescribed for numerous key immune cell targets.[14]

Decreased immunogenicity correlates with human MAbs, termed *umab*, which consist of fully human Fc and Fab regions; but it increases gradually and progressively with humanized MAbs, termed *zumab* or *xizumab*, consisting of human Fc and a mixture of human and mouse Fab regions; chimeric MAbs, termed *ximab*, consisting of human Fc and a fully mouse Fab region; and fully murine antibodies, termed *omab*, which have the most immunogenicity and consist of mouse Fc and Fab regions.[15]

MAbs target a variety of immune epitopes and are used clinically to exert their intended immune effects through 5 unique mechanisms. MAbs can act as ligand (an immune molecule) blockades, preventing ligands from activating their cognate receptors, which are typically used to stimulate some cell function. They can also block receptors on cell surfaces that inhibit receptor activation. In addition, cell surface receptor binding of MAbs can result in internalization and downregulation to limit other cell surface receptors from cell activation. The binding of MAbs can result in depletion of antigen-bearing cells through complement-mediated and Fc receptor IgG-mediated clearance. Finally, MAbs can induce active signals, called *signaling induction*, that alter cellular fates, such as apoptosis, or programmed cell death.[16]

Table 1 describes the year each drug was approved by the FDA, its estimated annual cost, and designated pregnancy category. Table 2 further defines the FDA's 5 pregnancy categories.

Abatacept

Abatacept is not a MAb; it is a fusion protein, termed *cept*, that prevents full T cell activation by preventing APCs from delivering the costimulatory signal to T cells via receptor blockade through competitively binding T cell protein CD 80/86. For T cells to turn on—that is, recognize and begin an immune response against any particular antigen (self or nonself)—an APC must secure 2 separate cell-binding sites: the CD28 receptor located on the T cell and the CD80/86 receptor located on the APC that houses the MHC molecule.[17]

Abatacept is indicated for 6- to 17-year-olds with moderate to severe active polyarticular juvenile idiopathic arthritis (JIA) and for adults with RA not controlled by anti–TNF-α therapy. Moderate JIA is defined as between 6 and 20 inflamed joints, with no inflammation in other tissues, elevated erythrocyte sedimentation rate or C-reactive protein levels, a positive rheumatoid factor test or anticyclic citrullinated peptide antibodies, and/or evidence of inflammation, but no evidence on x-rays of bone damage. Severe JIA is defined similarly to moderate JIA but with more than 20 persistently inflamed joints or a rapid loss of functional abilities, anemia related to chronic illness, a low serum albumin level, evidence on x-ray of bone and cartilage damage, and inflammation in tissues other than joints.

Abatacept is administered as a 30-minute intravenous (IV) infusion of between 500 mg and 1000 mg, depending on the patient's weight, once every 2 weeks for 3 loading doses followed by once-monthly dosing until the desired clinical response is obtained.[18] This drug may also be given subcutaneously, if indicated.

Side effects of abatacept can include allergic reactions, serious infections, hepatitis B, tuberculosis (TB) reactivation, upper respiratory tract infections, headache, nausea, vomiting, dizziness, sore throat, and malignancies. Table 3 lists the 2009 guidelines of the American Association for the Study of Liver Diseases for managing patients with hepatitis B activation. As a result, it is important not to administer abatacept concurrently with other drugs that severely impair the immune system, such as anakinra, rituximab, tocilizumab, or other TNF-α inhibitors. Finally, patients who

TABLE 1

Drug Information[18,22,30,33,35,36,38,42,44,46,49,51,54,57]

Drug	Year Approved	Estimated Annual Cost	Pregnancy Category
Abatacept	2005	$22K	C
Rituximab	1997	$11.6K	C
Infliximab	1998	$25.7K	B
Etanercept	2002	$16K	B
Adalimumab	2008	$19.5K	C
Golimumab	2009	$23K	B
Certolizumab pegol	2008	$22K	B
Anakinra	2001	$15K	B
Tocilizumab	2010	$24K	C
Natalizumab	2006[a]	$28.4K	C
Alemtuzumab	2007[b]	$5K[c]	B
Belimumab	2011	$35K	C
Ustekinumab	2009	$16K	B
Omalizumab	2003	$6K-$24K	B

[a] *Second approval.*
[b] *Withdrawn.*
[c] *Subject to change.*

receive abatacept should avoid live vaccines until the drug is discontinued.

Rituximab

Rituximab is a B-cell–depleting chimeric anti-CD20 (a B lymphocyte-specific molecule beginning at the pre–B-cell stage) MAb, composed of both murine and human portions.[19] Once rituximab attaches to a B cell expressing the CD 20 marker, one or more antibody-dependent mechanisms occur to destroy the cell, such as Fc receptor gamma-mediated antibody-dependent cytotoxicity, complement-mediated cell lysis, growth arrest, and/or B cell apoptosis.[20]

Rituximab is indicated for previously untreated follicular, CD20-positive, B cell non-Hodgkin's lymphoma in combination with first-line chemotherapy; RA; granulomatosis with polyangiitis (GPA or Wegener's, a form of vasculitis that affects small- and medium-sized vessels in many organs); and microscopic polyangiitis, as well as for MS, SLE, and others (off-label).

Rituximab is dosed for autoimmune disorders at 1000 mg IV infusion titrated over several hours, with the first dose requiring careful attention to frequent vital signs and physical assessment, looking for signs and symptoms of a potential hypersensitivity reaction that could progress to anaphylactic shock. Proper titration of the first dose of rituximab involves starting the infusion slowly at 50 mg/h and then increasing the continuous rate by 50 mg/h every 30 minutes, with a maximum rate of 400 mg/h in the absence of signs and symptoms of hypersensitivity reactions including fever, shaking chills, flushing, itching, alterations in heart rate or blood pressure, dyspnea or chest discomfort, back or abdominal pain, nausea, vomiting, diarrhea, and various types of skin rashes. Table 4 highlights several key steps nurses can take to manage patients experiencing hypersensitivity reactions.[21]

TABLE 2

FDA Pregnancy Category Definitions[58]

A	Studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy. No evidence of risk in later trimesters.
B	Animal reproduction studies have failed to demonstrate a risk to the fetus. No adequate studies have been done in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus, no adequate studies have been done in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	Positive evidence of human fetal risk based on adverse reaction data from experience or human studies, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or positive evidence of human fetal risk based on adverse reaction data from experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.

TABLE 3

2009 Hepatitis B Reactivation Guidelines From the American Association for the Study of Liver Diseases[59]

Test for HBsAg and anti-HBc before immunosuppressive therapy in patients at high risk for HBV.
If the patient is HBsAg positive, further testing should include HBeAg, anti-Hbe, and an HBV DNA level.
Begin prophylactic antiviral therapy for HBV carriers at the onset of immunosuppressive therapy.
Provide prophylactic treatment for 6 months after immunosuppressive therapy in patients with baseline HBV DNA $<$ 2000 IU/mL.
Continue treatment for at least 12 months after withdrawal of rituximab. (There are no current national anti-TNF guidelines.)
Administer lamivudine or telbivudine if treatment course is $\leq$12 months with undetectable HBV DNA.
Administer tenofovir or entecavir if treatment course is $>$12 months.
Avoid interferon-α because of immunosuppressive effect.
Restart antiviral therapy in HBsAg-positive patients who develop a hepatitis flare considered due to HBV, if they are immunosuppressed.

Approximately 30 minutes before administering rituximab, the nurse should medicate the patient with acetaminophen and diphenhydramine. The nurse should be prepared to interrupt the infusion if signs and symptoms of a hypersensitivity reaction are observed. Methylprednisolone IV, normal saline IV fluid, and emergency equipment should be readily available. The second dose typically occurs on day 15. If the patient did not have a hypersensitivity reaction during the first dose, subsequent rates can be initiated at 100 mg/h and increased by 100 mg/h every 30 minutes to a maximum rate of 400 mg/h. Doses of rituximab may be repeated in 6 to 12 months, until the desired clinical response is obtained.

TABLE 4

Nursing Management of Hypersensitivity Reactions[21]

1. Stop the infusion of the suspected medication.
2. Administer an intramuscular injection of epinephrine.
3. Call for help. Summon a resuscitation team in a hospital setting or call 911 in a community setting.
4. Place the patient in a supine position, if tolerated, to maintain blood flow to vital organs.
5. Provide supplemental oxygen.
6. Administer volume resuscitation.
7. Start intravenous antihistamines.
8. Provide close observation.
9. Take frequent vital signs.
10. Document.
11. Re-premedicate with appropriate drugs as ordered.
12. Restart medication at a slower rate than initially.
13. Titrate slowly as tolerated until completed.
14. Provide specific discharge instructions to the patient and family.

Side effects of rituximab can include signs and symptoms of immediate hypersensitivity reaction described previously, which may occur as long as 24 hours after infusion; hypotension; bacterial and viral infections, especially hepatitis B reactivation; a variety of cardiovascular, renal, and gastrointestinal effects; as well as a risk for developing progressive multifocal leukoencephalopathy (PML).[22]

PML is a rare, incurable, and usually fatal viral disease of the brain caused by the John Cunningham (JC) virus, which is named after the first person in which the disease was discovered in 1971. PML is characterized by progressive damage or inflammation of the brain's subcortical white matter in the parietal and occipital lobes. It occurs almost exclusively in patients with severe immunodeficiency and leads to rapid demyelination. Some 39% to 58% of the general population possess serum JC virus antibodies.[23,24] Diagnosis of PML occurs by measuring viral DNA in the cerebral spinal fluid and/or through magnetic resonance imaging. Discontinuing the causative agent and providing supportive care are the only helpful options, but do not necessarily prevent death.

TUMOR NECROSIS FACTOR

Almost all nucleated cell types in the body possess tumor necrosis factor (TNF) receptors and can potentially react to TNF stimuli. TNF is mostly secreted by monocytes and macrophages. It is a cytokine, or chemical messenger, whose family can cause apoptosis, cytokine suppression, complement-dependent cytotoxicity, and antibody-dependent

cell-mediated cytotoxicity.[25] TNF has numerous effects; however, it plays a central role in inflammation and immunity and is most notably responsible for tumor regression, septic shock, and cachexia.

Cells that interact with TNF have proteins that protrude through the cell's membrane, called TNF ligands, that can communicate or signal back to other immune cells through the binding of their cognate receptors. Examples of these effects include (1) brain fever and hormones; (2) bone resorption; (3) liver-acute-phase proteins and IL-6 secretion; (4) endothelium-adhesion molecules, microvascular permeability, coagulation factors, and cytokines; (5) monocytes and macrophages-TNF, IL-1, IL-6, MHC class II; (6) fibroblasts proliferation, IL-6, IL-8, IFN beta, prostaglandin, and collagenase; (7) adipocyte inhibition of lipoprotein lipase; (8) polymorphonuclear leukocytes adhesion, oxidative burst, hydrogen peroxide production; (9) B cells differentiation; and (10) T cells-IL-2, IFN gamma, granulocyte-macrophage colony-stimulating factor, and proliferation.[26]

TNF INHIBITORS

TNF inhibitors, or anti-TNF drugs, have become the standard treatment concerning resistance to initial disease-modifying antirheumatic drug (DMARD) therapy for RA. Meta-analyses and other randomized trials have shown that anti-TNF monotherapy is similar in efficacy compared with methotrexate (MTX, a chemotherapeutic agent considered a DMARD) alone and that its combination with MTX significantly reduced disease activity and slowed radiographic progression to a greater extent than anti-TNF monotherapy or MTX monotherapy.[27,28] Only 5 TNF inhibitors have been FDA approved to date; they include infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol.[29] Although their overall effects in binding and neutralizing TNF to halt further inflammation are similar, each drug possesses subtle physical differences and slightly different side-effect profiles that can help guide health care practitioners in selecting the best drug choice for the individual patient, based on their unique circumstances, comorbidities, clinical experience, regulatory issues, insurance, preferred route, and cost limitations.

Infliximab

Infliximab is a chimeric MAb directed against TNF. It was approved by the FDA in 1998 and is currently indicated for adult and pediatric CD, adult and pediatric UC, RA, AS, spondylitis psoriatic arthritis, and plaque psoriasis. It is dosed between 3 and 10 mg/kg every 6 to 8 weeks as an IV infusion over 2 hours and continued until the desired clinical response.[17]

Because of its potential for serum sickness, the patient should be premedicated with acetaminophen and diphenhydramine approximately 30 to 90 minutes before administration. It's important to follow institution-based guidelines for managing infusion-related reactions. For mild infusion reactions, infliximab can be slowed to 10 mL/h with frequent (every 10 minutes) assessments of the patient's vital signs and a normal saline bolus (500-1000 mL wide open or 500 mL to 1 liter at a rate of up to 999 mL/h due to IV pump rate restrictions) initiated. After about 20 minutes, the rate can be slowly titrated upward by 20 mL/h every 15 minutes in the absence of further reactions to a maximum rate of 125 mL/h.

For moderate and severe reactions, stop the drug immediately, notify the prescribing health care practitioner, administer a steroid IV push as prescribed, start a normal saline bolus, and monitor and document the patient's vital signs every 5 minutes until resolved. Nurses must ensure that emergency medications used to treat hypersensitivity reactions are readily available. Infliximab also requires an in-line low-protein binding filter. Some patients can develop antibodies to infliximab. If this occurs, there is a greater potential for hypersensitivity reactions requiring further workup to identify infliximab antibodies, adding a steroid to the premedication plan, or possibly discontinuing the agent and switching to another drug in the TNF inhibitor family.[30]

Etanercept

Etanercept is a soluble p75 TNF receptor fusion protein that consists of 2 separate binding sites for TNF bound to an Fc portion of IgG.[28,31] It functions as a TNF binding site decoy.[32] Etanercept was approved by the FDA in 2002 and is currently indicated for RA, polyarticular JIA, psoriatic arthritis, AS, and plaque psoriasis.

Etanercept is a subcutaneous (SC) injection dosed at 25 to 50 mg once a week.[33] Although it is usually administered by the patient, initial doses are given by a nurse who begins proper SC administration teaching. The autoinjector requires refrigeration during storage; waiting 15 minutes until it reaches room temperature before administration minimizes injection discomfort. In addition, chronic SC injections require alternating appropriate sites. Finally, those who handle the etanercept should avoid shaking or freezing the medication to prevent damage or a reduction in the effectiveness of the intended dose.

Adalimumab

Adalimumab is a fully human MAb that binds TNF. It is associated with a lower risk for developing antidrug antibodies because of its human construction.[34] Adalimumab was approved by the FDA in 2008 and is indicated for RA, JIA, CD, AS, psoriatic arthritis, and chronic plaque psoriasis; in 2012, it was approved for UC when unresponsive to immunosuppressants. It

requires a loading dose between 80 and 160 mg and is subsequently dosed at 40 to 80 mg SC, depending on exact indication every 2 weeks, until the desired clinical response.[35] Similar SC precautions and practices regarding etanercept also apply to adalimumab.

Golimumab

Golimumab is biologically and molecularly similar to adalimumab, as a human IgG1 kappa MAb directed against TNF that binds and neutralizes its effects.[28] It was FDA approved in 2009 and has current indications for in-combination use with MTX for treating RA; used alone or combined with MTX for treating psoriatic arthritis and AS; and pending FDA approval for UC. It is dosed between 50 and 100 mg SC every 4 weeks until the desired clinical response.[36] Similar SC precautions and practices to etanercept and adalimumab also apply to golimumab. One minor difference is that the autoinjector developed for golimumab uses 2 clicks instead of 1 for successful SC administration. Golimumab should not be used in combination with any other biologic DMARD because of increased immune toxicity.

Certolizumab pegol

Certolizumab pegol is unique in the TNF inhibitor family. It is composed solely of a human Fab fragment that is chemically linked to polyethylene glycol, an alternative starting material to water that allows a slowed clearance of the carried protein from the blood, a longer-acting medicinal effect and reduced toxicity, and longer dosing intervals.[29,37] Because polyethylene glycol does not cross the placenta, it can be used to treat pregnant women with RA or CD. Its lack of the Fc portion on the MAb, however, does not induce complement activation, antibody-dependent cellular toxicity, or apoptosis. Like other TNF inhibitors, certolizumab pegol's main effect is neutralizing membrane-associated and soluble TNF particles. It has been approved by the FDA for CD and RA, and it is dosed at 400 mg SC every 2 weeks or once every 4 weeks for maintenance until the desired clinical response.[28,38]

Side Effects of TNF Inhibitors

The majority of side effects of TNF inhibitors are minor. They include injection site reactions with those administered SC, headaches, rashes, and stomach pains that are easily managed. Serious, but less common, side effects include neutropenia with a risk for bacterial sepsis and other possible fatal infections; a risk of developing opportunistic infections such as TB and non-TB mycobacterial infections; fungal infections; hepatitis B; and varicella zoster viral reactivation. In general, patients should avoid live vaccines, smoking, and pregnancy when receiving any of these medications.

Patients receiving TNF inhibitors are also more susceptible to food-borne infections, such as salmonella and listeria, and as a result, should avoid consuming raw eggs, undercooked meats and poultry, and unpasteurized dairy products. An induction of autoimmunity also has been noted with the development of autoantibodies on rare occasions that can result in lupus-like syndromes and demyelinating diseases.

Cutaneous reactions, including rashes and pruritus, have been commonly reported. Recently, an increased prevalence of specific congenital abnormalities has been noted in babies of women treated with etanercept and infliximab during pregnancy.[39]

Additional significant side effects include worsening of heart failure, serious infusion reactions (with infliximab-serum sickness), and possible malignancies. Recent evidence suggests, however, that the risk of developing malignancies—specifically lymphoma and other lymphoproliferative disorders—was caused primarily by other immunosuppressants that were administered concurrently in these patients or as the result of higher levels of autoimmune disease activity itself.[40] Finally, some patients treated with infliximab have developed PML.

Anakinra

Anikinra is a nonglycosylated recombinant human IL-1 receptor antagonist produced in *Escherichia coli*. IL-1 is primarily produced by activated macrophages, neutrophils, epithelial cells, and endothelial cells and is responsible for eliciting inflammation, fever, and sepsis. Fibroblasts, endothelial cells, T and B cells, and neurons all respond to IL-1 by recruiting more immune cells to the site of inflammation.

In RA, IL-1 signal transduction stimulates bone resorption in cartilage and bone cells to induce tissue damage. Anakinra prevents membrane-bound and circulating IL-1 binding, preventing signal transduction to limit these effects.[41] It is indicated to inhibit the progression of structural damage in adults with moderate to severe RA in the absence of clinical improvement or inadequate response to DMARDs. Other indications for anakinra include cryopyrin-associated periodic syndromes (CAPS) or neonatal-onset multisystem inflammatory disease.

Anakinra is dosed at 20 to 100 mg SC daily for up to 2 years for adults with RA and at 1 to 2 mg/kg SC daily titrated upward over several months to a maximum of 8 mg/kg SC daily for CAPS.[42] Common side effects include allergic reactions, injection site reactions, serious infections, malignancies, nausea, vomiting, diarrhea, headache (HA), and sinusitis. Complete blood counts, kidney function tests, and screening for neutralizing antibodies should be monitored closely in patients receiving anakinra. Finally, patients treated with anakinra should avoid live vaccines and notify their health care provider of any signs or symptoms of active infections.

OTHER MONOCLONAL ANTIBODIES

Tocilizumab

Tocilizumab is a humanized MAb against the IL-6 receptor, which normally acts as a proinflammatory and anti-inflammatory cytokine responsible for multiple biologic activities. IL-6 is secreted primarily by T cells and macrophages to stimulate the immune response to promote inflammation but is also secreted by osteoblasts, which then stimulate osteoclast formation, causing bone breakdown commonly found in RA. The IL-6 receptor system involves 2 chains, 2 particles of glycoprotein 130, which sandwich the IL-6 receptor.[43] When IL-6 binds to this receptor, signal transduction occurs and results in gene expression, cell differentiation, the production of acute phase proteins, the reduction of iron and zinc concentrations, Ig induction in B cells, cytotoxic T-cell differentiation, and finally, differentiation of osteoclasts, angiogenesis, and collagen formation.[43] Tocilizumab physically sits on the IL-6 receptor and subsequently blocks these effects. It is indicated for adults with RA with or without MTX and in children with SJIA.

Tocilizumab is dosed at 4 mg/kg and titrated up to 8 mg/kg, based on the desired clinical response, with a maximum of 800 mg per infusion for patients with RA. It may take 6 to 12 weeks to elicit a clinical response in some individuals. Tocilizumab is administered as an IV infusion over the course of 1 hour once every 4 weeks. In children with SJIA, tocilizumab is dosed based on the patient's weight: for less than 30 kg at 12 mg/kg IV infusion over 1 hour every 2 weeks and for greater than 30 kg at 8 mg/kg similarly.[44]

Common side effects of tocilizumab include hypersensitivity reactions; serious and even fatal opportunistic infections, such as pneumonia, bronchitis, and polynephritis; and unusual infections, such as TB, fungal, hepatitis B, and varicella-zoster virus reactivation. Malignancies have been reported in patients treated with tocilizumab, along with an increased risk of bleeding due to thrombocytopenic effects, potential for bowel perforation, and an increase in both cholesterol levels and liver function tests.

Natalizumab

Natalizumab is recombinant MAb directed against alpha-4 integrins, which are expressed on the surface of inflammatory lymphocytes and monocytes used to gain access from the bloodstream through vascular adhesion and diapedesis, which is the movement of the inflammatory cells into the brain parenchyma or other structures.[45]

Natalizumab's main action is through receptor blockade disallowing the necessary interaction between alpha-4 integrin on immune cells with vascular adhesion molecule-1 on endothelial cells, resulting in a significant reduction of access of immune cells into the brain, as in the case of MS, or into the lining of the gut, as with CD. Natalizumab is indicated for the treatment of both of these diseases. It is dosed at 300 mg as an IV infusion over 1 hour once a month. It is not to be given as IV push or IV bolus, or in patients with a preexisting weak immune system. Because the drug is reconstituted from a fragile protein powder, shaking the vial, which could destroy the drug particles, should be avoided. In addition, it is important to administer natalizumab within 8 hours of preparation.

Rare occurrences of PML have been reported in patients treated with natalizumab, which led to a voluntary drug withdrawal from the market. However, in 2006 it was reintroduced with a special prescribing tool to better identify patients who are at greater risk for developing PML. Called the TOUCH prescribing program, the tool is now required for all potential patients.

Common side effects of natalizumab include hypersensitivity reactions, such as fever, fatigue, HA, rash, urticaria, arthralgia, dyspnea, and muscle cramps, which can be managed as discussed with rituximab.[46] Other side effects may include infections such as sore throat, night sweats, urinary tract infections (UTIs), hepatitis B reactivation, and PML. Neutralizing antibodies can also develop over time, limiting the effectiveness of the drug as well as increasing the incidence of infusion reactions. Swelling in the upper and/or lower extremities, including significant weight gain, N/V/D, heartburn, and constipation, have also been reported in patients receiving natalizumab.

Alemtuzumab

Alemtuzumab is humanized MAb directed against CD 52, a protein present on the surface of mature lymphocytes but absent on lymphocyte stem cells.[47] The binding of the MAb leads to antibody-mediated cytotoxicity and complement-mediated cell lysis or removal/depletion of marked cells from the circulation.[48]

Although alemtuzumab was an FDA-approved anticancer therapy and part of several conditioning regimens to prevent rejection in organ and stem cell transplantation, it was taken off the market, and its license was surrendered in August 2012. This was in preparation for a relaunch under a different name to position it as a potential primary indication for MS, pending 2 phase III clinical trials. The drug continues to be available for anticancer and transplant uses until existing supplies run out, but it now requires a special patient access program.

In the MS clinical trials, alemtuzumab was initially dosed at 3 mg IV infusion over 2 hours daily and increased to 12 to 24 mg, with a maximum dose of 30 mg, over 3 to 5 days followed by 1 year off. The second dose was administered as an IV infusion once daily over 3 days and then 1 to 2 years off.

Alemtuzumab should not be administered as IV push or IV bolus, nor should the fragile protein be shaken at any time during reconstitution. Appropriate

premedications and prophylactic medications should be ordered and administered to prevent hypersensitivity reactions and opportunistic infections.[49]

Common side effects of alemtuzumab include potential cytopenias and fatal infections, including pneumocystis pneumonia caused by the fungus *Pneumocystis jirovec*, herpes simplex virus 1 and 2, cytomegalovirus, and hepatitis B reactivation. Infusion reactions marked by fever, chills, dizziness, muscle stiffness, HA, rashes, tiredness, N/V/D, and/or dyspnea have been reported in many patients. The development of autoimmune thyroid disease, or Graves' disease, as well as autoimmune idiopathic thrombocytopenic purpura and hemolytic anemia, have been observed.[49]

Belimumab

Belimumab is a human MAb that inhibits B-cell activating factor, also known as B-lymphocyte stimulator. It prevents B cells from turning into mature plasma cells, which produce antibodies and are responsible for memory and secondary immune responses to specific antigens-autoantibodies in the case of SLE.[50] Belimumab is indicated for antibody-positive, low-complement SLE as an add-on therapy to other immunosuppressants; phase III trials, however, excluded more severe cases of SLE with kidney and brain damage. Therefore, it should be used with extreme caution in these cases. Belimumab also failed to show any benefit for African Americans, was deemed only marginally effective by the FDA, and was not studied concurrently with cyclophosphamide. Some benefit was noted for patients with Sjörgren's syndrome, but no benefit was observed in patients with RA. Belimumab is dosed at 10 mg/kg as an IV infusion over 1 hour every 2 weeks for 3 loading doses, followed by once every 4 weeks thereafter for maintenance therapy.[51]

Common side effects include hypersensitivity reactions that include fever, chills, HA, and other signs and symptoms noted previously. Premedications with antihistamines, antipyretics, and corticosteroids should be administered approximately 30 minutes before starting the drug infusion. Severe infections, including fatal infections resulting from leukopenia, have been observed and include UTIs, nasopharyngitis, cough, sore throat, and hepatitis B reactivation. Live vaccines should be avoided in patients receiving belimumab treatments. Other side effects include N/V/D, insomnia, and stomach, arm, and leg pain. Anxiety, depression, and suicidal ideation have also been reported. Although malignancies have been observed in many patients treated with belimumab, these are thought to be caused by other immunosuppressants.[51]

Ustekinumab

Ustekinumab is a human MAb directed against IL-12 and IL-23, naturally occurring cytokines (proteins) secreted by dendritic cells (APCs) that stimulate NK and T cells to regulate the immune system and other inflammatory disorders.[52] IL-12 and IL-23 normally activate NK and T cells through intracellular signaling, which then become directly involved in the pathogenesis of plaque psoriasis, a common autoimmune disorder affecting the skin's epidermis and dermis layers.[53] These immune cells mistake skin cells for a pathogen, send out faulty signals, and cause hyperproliferation, or buildup, of skin cells manifested as raised silvery-white patches. Ustekinumab binds to the p40 subunit of both IL-12 and IL-23 and acts as a ligand blockade halting the progression of autoimmunity.

Ustekinumab is approved for the treatment of moderate to severe plaque psoriasis; moderate-stage plaque psoriasis is defined as affecting 3% to 10% of the body, whereas severe plaque psoriasis affects more than 10% of the body.

Ustekinumab is initially dosed at 45 to 90 mg SC once, depending on the patient's weight—less than or equal to 100 kg or greater than 100 kg, respectively—followed by a second loading dose 4 weeks later, then once every 3 months for maintenance or until the desired clinical response, which may take up to 12 weeks.[54] It is supplied in a 90-mg/mL prefilled, single-use syringe, which should be refrigerated until administration. Allow 30 minutes for the syringe and solution to reach room temperature, to lessen the injection site discomfort. It should also be protected from light and never frozen.

Common side effects of ustekinumab include hypersensitivity and injection site reactions, fatigue, weakness, and even mouth and throat ulcers. Serious infections have been observed, including upper respiratory infections and TB. Live vaccines should be avoided in patients during treatment. Malignancies, especially some forms of skin cancer, have been reported. Finally, reversible posterior leukoencephalopathy syndrome—or posterior reversible encephalopathy syndrome (PRES), a rare condition that causes edema in the brain and can lead to death—has occurred in some patients who were treated with ustekinumab. Headaches, seizures, confusion, and vision problems could indicate early signs and symptoms of PRES.[54]

Omalizumab

Omalizumab is a humanized MAb directed against IgE antibodies, or anti-IgE Mab.[55] The typical allergic cascade includes the following: (1) an allergen is recognized by an APC; (2) the APC then stimulates a T cell; (3) that T cell secretes cytokines to recruit B cells; (4) memory B cells—also called plasma cells, a B-cell subtype—generate IgE (antibodies); (5) unbound IgE stimulates mast cells and basophils; and (6) mast cells and basophils produce and release inflammatory mediators, such as histamine, prostaglandins, and leukotrienes, which attract other immune cells to the site.[56]

Omalizumab prevents the activation and release of allergic mediators in both the early and late phases of allergic responses. Omalizumab is indicated for adolescents 12 years and older and adults who suffer from moderate to severe persistent asthma, which is defined as having daily symptoms, and who have signs and symptoms that are inadequately controlled with inhaled corticosteroids.

It is dosed at 150 to 375 mg SC every 2 to 4 weeks, depending on serum IgE levels or until the desired clinical response. It should be injected slowly over 5 to 10 seconds. Dosing should not exceed 150 mg per site per injection. The patient's body weight and total serum IgE levels should be monitored frequently to adjust dosing requirements. Because omalizumab is a fragile protein, the vial should not be shaken. If reconstituting, allow the lyophilized product to dissolve for 15 to 20 minutes before drawing up the solution in the syringe to be used for the SC injection.

The primary adverse effect of omalizumab is anaphylaxis, a life-threatening systemic allergic reaction noted as a black-box warning on the drug's label. Anaphylaxis is not necessarily related to the drug, but it could be a response to the protein nature of the antibody in patients who already possess highly reactive immune systems to many different triggers. Signs and symptoms of anaphylaxis can include serum sickness, bronchospasm, hypotension, syncope, urticaria, and angioedema of the throat or tongue. Although the drug was once self-administered in the patient's home, current guidelines require it to be administered by health care professionals in health care facilities with immediate access to emergency equipment and other life-saving resources. Other common side effects of omalizumab include injection site reactions, HAs, viral infections, sinusitis, pharyngitis, and other upper respiratory infections. Malignancies such as breast, skin, parotid, and prostate cancers have also been reported, as have serious cardiovascular events.[57]

CONCLUSION

Many biologic agents are becoming more commonplace and are being incorporated into the treatment plans of patients suffering from autoimmune disorders, frequently because of the patient's lack of response to standard therapies. No national nursing standards exist for the safe administration of the drugs in the autoimmune population (for nononcologic purposes). In addition, no minimum practice competency guidelines have been identified specifically for nurses working with patients with autoimmune disorders. These should be swiftly defined, developed, and supported by evidence-based practices and communicated in the nursing literature. Adding to the complexity of this problem is the lack of a single, overarching authority or autoimmune organization designed to identify and support national nursing standards. As more and more experimental drugs progress through the FDA approval process, nurses need to continue to update their knowledge and resultant practice to ensure sufficient preparation, safe administration, high-quality patient care, and informed patient/family education regarding these drugs.

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