

Therapeutic Applications of Monoclonal Antibodies

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ABSTRACT

Monoclonal antibodies drive the development of multibillion dollar biotechnology industry. Many of the pharmaceuticals companies have entered monoclonal antibodies sector, attracted by quicker and less costly development, higher success rates, premium pricing, and potentially reduced threats from generics. The ideal treatment of rheumatoid arthritis (RA) should be safe, produce sustained disease remission and stop radiological damage after a brief course of treatment. If repeated treatments are necessary, they must be safe and economical to use in the long term. It is against these criteria that new treatments for RA, including mAb, should and will be assessed. Monoclonal antibodies are used in the treatment of cancer, including leukemia, colorectal cancer, breast cancer and non-Hodgkin's lymphoma, RA, ischemic heart disease and transplant rejection.

Introduction

Substances foreign to the body, such as disease-causing bacteria and viruses and other infectious agents, known as antigens, are recognized by the body's immune system as invaders. Our natural defenses against these infectious agents are antibodies, proteins that seek out the antigens and help destroy them.^[1,2]

Antibodies have two very useful characteristics. First, they are extremely specific, that is, each antibody binds to and attacks one particular antigen. Second, some antibodies, once activated by the occurrence of a disease, continue to confer resistance against that disease; classic examples are the antibodies to the childhood diseases chickenpox and measles. It is the first trait of antibodies, their specificity, that makes monoclonal antibody technology so valuable. Not only can antibodies be used therapeutically to protect against disease but also they can also help to diagnose a wide variety of illnesses and can detect the presence of drugs, viral and bacterial products, and other unusual or abnormal substances in the blood.^[3]

Cancer therapy

Cancer Immunotherapy is the use of the immune system to reject cancer. The main premise is stimulating the patient's immune system to attack the malignant tumor cells that are responsible for the disease. This can be either through immunization of the patient, in which case the patient's own immune system is trained to recognize tumor cells as targets to be destroyed, or through the administration of therapeutic antibodies as drugs, in which case the patient's immune system is recruited to destroy tumor cells by the therapeutic antibodies.^[4]

Drugs used in cancer

Leukemia

Alemtuzumab:^[5,6] Alemtuzumab is a recombinant DNA-derived humanized monoclonal antibody (Campath-1H) that is directed against the 21–28 kDa cell surface glycoprotein, CD52. Gemtuzumab is also used in the treatment of leukemia.

Indications and use: Alemtuzumab is indicated for the treatment of B-cell chronic lymphocytic leukemia (B-CLL) in patients who have been treated with alkylating agents and in whom fludarabine therapy has failed.

Contraindications and precautions: Alemtuzumab is contraindicated in patients who have active systemic infections, underlying immunodeficiency (e.g., seropositive for HIV), or known Type I hypersensitivity or anaphylactic reactions to Campath or to any one of its components.

Adverse reactions: Alemtuzumab has been associated with hypotension, rigors, fever, shortness of breath, bronchospasm, chills, and/or rash. In postmarketing reports, the following serious infusion-related events were reported: syncope, pulmonary infiltrates,

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respiratory arrest, cardiac arrhythmias, myocardial infarction and cardiac arrest.

Colorectal cancer

Bevacizumab:^[7,8] Bevacizumab is a humanized monoclonal antibody and was the first commercially available angiogenesis inhibitor. It stops tumor growth by preventing the formation of new blood vessels by targeting and inhibiting the function of a natural protein called vascular endothelial growth factor (VEGF) that stimulates new blood vessel formation. The drug was first developed as a genetically engineered version of a mouse antibody that contains both human and mouse components. Other drugs for treatment of colorectal cancer are cetuximab and panitumumab.

Clinical use: Bevacizumab was approved by the Food and Drug Administration (FDA) in February 2004 for use in colorectal cancer when used with standard chemotherapy treatment. It was approved by the EMA (European medicines agency) in January 2005 for use in colorectal cancer. Israel has also approved the use of bevacizumab.

Bevacizumab is usually given intravenously through the arm every 14 days. In colon cancer, it is given in combination with the chemotherapy drug 5-fluorouracil (5-FU), leucovorin, and oxaliplatin or irinotecan. Bevacizumab has also demonstrated activity in renal cell cancer and ovarian cancer when used as a single agent, and in lung cancer and breast cancer when combined with chemotherapy.

Side effects: The main side effects of concern are hypertension and heightened risk of bleeding. Bowel perforation has also rarely been reported. Studies done particularly in lung cancer have shown that less than half of the patients with advanced disease qualify for treatment with this drug.

The FDA updated the label on the drug on September 25, 2006, to note rare cases of brain capillary leak syndrome and nasal septum perforation.

Breast cancer

Tumor cells display cell surface receptors that are rare or absent on the surfaces of healthy cells, and which are responsible for activating cellular signal transduction pathways that cause the unregulated growth and division of the tumor cell. Examples include ErbB2, a constitutively active cell surface receptor that is produced at abnormally high levels on the surface of breast cancer tumor cells.

Trastuzumab:^[9-12] Trastuzumab is a humanized monoclonal antibody which binds to the extracellular segment of the erbB2 receptor.

Mechanism of action: Cells treated with trastuzumab undergo arrest during the G1 phase of the cell cycle and so there is reduced proliferation. It has been suggested that trastuzumab induces some of its effects by downregulation of erbB2, leading to disruption of receptor dimerization and signaling through the downstream PI3K cascade. P27Kip1 is then not phosphorylated and is able to enter the nucleus and inhibit cdk2 activity, causing cell cycle arrest. Also, trastuzumab suppresses angiogenesis by both induction of antiangiogenic factors and repression of proangiogenic factors. It is thought that a contribution to the unregulated growth observed in cancer could be due to proteolytic cleavage of erbB2 that results in the release of the extracellular domain. Trastuzumab has been shown to inhibit erbB2 ectodomain cleavage in breast cancer cells. There may be other undiscovered mechanisms by which trastuzumab induces regression in cancer.

Side effects:^[13,14] Trastuzumab is associated with cardiac dysfunction

in 2–7% of cases. Approximately 10% of patients are unable to tolerate this drug because of pre-existing heart problems; physicians are balancing the risk of recurrent cancer against the higher risk of death due to cardiac disease in this population. The risk of cardiomyopathy is increased when trastuzumab is combined with anthracycline chemotherapy (which itself is associated with cardiac toxicity). Trastuzumab costs about \$70,000 for a full course of treatment.

Rituximab

Mechanism of action:^[13,15-17] The antibody binds to the cluster of differentiation 20 (CD20). CD20 is widely expressed on B cells. It does not shed, modulate or internalize. Although the function of CD20 is relatively unknown, it has been indicated that CD20 could play a role in Ca²⁺ influx across plasma membranes, maintaining intracellular Ca²⁺ concentration and allowing activation of B cells. Also, apart from the Fc portion-mediated antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC), the exact mode of action of rituximab is unclear, but it has been found to have a general regulatory effect on the cell cycle and to increase major histocompatibility complex (MHC) II and adhesion molecules LFA-1 and LFA-3 (lymphocyte function-associated antigen), elicit shedding of CD23, downregulate the B cell receptor, and induce apoptosis. The combined effect results in the elimination of B cells (including the cancerous ones) from the body, allowing a new population of healthy B cells to develop from lymphoid stem cells.

Adverse effects: Infections (hepatitis B reactivation, other viral infections) and progressive multifocal leukoencephalopathy (PML), immune toxicity, with depletion of B cells in 70–80% of patients with non-Hodgkin's lymphoma, pulmonary toxicity.

Other uses are in rheumatoid arthritis (RA), Evans syndrome, and autoimmune disease. Other drugs used are ibritumomab and tositumomab.

Rheumatoid arthritis therapy

Monoclonal antibodies bind to their targets with a high specificity and therefore have excellent potential as therapeutic agents. Monoclonal antibodies targeting mediators of synovitis have been tested in clinical trials over the last decade.^[18,19] Anti-cytokine therapies, in particular anti-tumor necrosis factor (TNF) alpha monoclonal antibodies, suppressed inflammation and produced rapid symptomatic improvement. Anti-lymphocyte monoclonal antibodies produced long-lasting disease suppression in animal models of RA. The use of depleting anti-lymphocyte monoclonal antibodies in RA had been disappointing as they did not penetrate the synovial joint in sufficient quantity to suppress disease without producing severe and protracted peripheral blood lymphopenia. Consequently, their use in RA had been abandoned. In contrast, clinical trials of non-depleting anti-CD4 monoclonal antibodies in RA showed that they could suppress synovitis.

Classification

- Tumor necrosis factor inhibitors: etanercept (Enbrel[®]), adalimumab (Humira[®]), and infliximab (Remicade[®])
- T-cell costimulatory blocking agents: abatacept (Orencia[®])
- B-cell depleting agents: rituximab (Rituxan[®])

Tumor necrosis factor inhibitors

The TNF inhibitors^[20-23] represent the first “rationally based” treatment, as well as the first FDA-approved recombinant proteins (“biologics”) for the treatment of RA.

Tumor necrosis factor- α (TNF- α) and interleukin-1 (IL-1) are the major macrophage-derived cytokines present in the rheumatoid joint and both induce the synthesis and secretion from synovial fibroblasts of matrix-degrading proteases, prostanoids, interleukin-6 (IL-6), interleukin-8 (IL-8) and granulocyte-macrophage colony stimulating factor (GM-CSF).

TNF- α is a pro-inflammatory cytokine produced by macrophages and lymphocytes. It is found in large quantities in the rheumatoid joint and is produced locally in the joint by synovial macrophages and lymphocytes infiltrating the joint synovium. TNF is one of the critical cytokines mediating joint damage and destruction due to its activities on many cells in the joint as well as effects on other organs and body systems.

Development of TNF inhibitor

The two strategies for inhibiting TNF consist of monoclonal anti-TNF antibodies and soluble TNF receptors (sTNF-R).^[24,25] Both constructs theoretically bind to circulating TNF- α , thus limiting its ability to engage cell membrane bound TNF receptors and activate inflammatory pathways. sTNF-R, but not anti-TNF antibodies, would also be expected to bind lymphotoxin.

The best studied of the monoclonal anti-TNF antibodies is infliximab (Remicade), originally referred to as cA2. Infliximab is a chimeric human/mouse monoclonal anti-TNF- α antibody composed of the constant regions of human (Hu) IgG1 κ , coupled to the Fv region of a high-affinity neutralizing murine anti-HuTNF- α antibody. The antibody exhibits high affinity (K_a 1010/mol) for recombinant and natural HuTNF- α , and neutralizes TNF-mediated cytotoxicity and other functions *in vitro*. Because of the potential for an immune reaction to the mouse protein components of a chimeric antibody, an alternate strategy has been to develop a fully human anti-TNF monoclonal antibody. One such antibody known as D2E7, also known as adalimumab, was generated by phage display technology. A high affinity murine anti-TNF monoclonal antibody was used as a template for guided selection, which involves complete replacement of the murine heavy and light chains with human counterparts and subsequent optimization of the antigen-binding affinity. D2E7 (Humira™) received FDA approval in December 2002.

These drugs are similar in their efficacy at decreasing signs and symptoms of RA, slowing or halting radiographic damage, and improving function and quality of life. These agents are also now approved for the treatment of other forms of inflammatory arthritis including psoriatic arthritis and ankylosing spondylitis. The first approved TNF- α blocker was etanercept (Enbrel) in May 1998. Then came infliximab (Remicade) in November 1999, while adalimumab (Humira) was approved in December 2002.

Infliximab (Remicade): Infliximab^[25-27] was the first monoclonal antibody to human necrosis factor alpha (TNF- α) developed for treating RA and for the treatment of psoriatic arthritis and ankylosing spondylitis, as well as psoriasis and Crohn's disease. This chimeric antibody binds with a high affinity to both soluble and trans-membrane TNF and is able to reduce synovial/joint inflammation, bone resorption and cartilage degradation. The efficacy of infliximab has been observed in active RA despite treatment with multiple disease modifying anti-rheumatic drugs

(DMARDs), and in early disease with no prior treatment by methotrexate (MTX). Recent data suggest that using infliximab early in RA treatment increases the percentage of clinical remission and allows infliximab discontinuation.

Infliximab is effective as monotherapy in reducing the signs and symptoms of RA but anti-infliximab antibodies can develop which can, in turn, reduce the durability of the response. Co-treatment with methotrexate reduces the frequency of these antibodies and is therefore recommended along with infliximab.

Mechanism of action: Infliximab binds TNF in the joint and in the circulation, preventing its interaction with TNF receptors on the surface of inflammatory cells, and eventually clearing TNF from the circulation. Monoclonal antibodies also bind to cell-bound TNF. Through its actions, infliximab inhibits the activity of TNF.

Dose: Infliximab is administered via the intravenous route. Infusions typically take between 2 and 3 hours. The recommended starting dose of infliximab is 3 mg/kg for RA given as an intravenous infusion followed by additional dosing at 2 and 6 weeks, then every 8 weeks thereafter. Infliximab should be given in combination with methotrexate.

Side effects: In clinical practice, infections are increased in patients who receive TNF antagonists, both mild and serious. In clinical trials, the frequency of serious infections was not found to be increased in infliximab + methotrexate groups compared to methotrexate alone groups. The risk for disseminated TB appears to be higher for infliximab than for etanercept, perhaps because of its longer half-life, due to activities against cell-bound TNF, due to lysis of target cells, or because of more at-risk patients having been exposed to the drug. All patients receiving a TNF inhibitor should be carefully and continuously monitored for signs of infection. Infliximab is not recommended in patients with congestive heart failure or with demyelinating disease.

Patients receiving infused biological agents including infliximab may develop a clinical syndrome of fever, chills, body aches, and headache associated with the infusion of the antibody. The development of antinuclear antibodies (ANA) and anti-double stranded DNA antibodies is seen with infliximab.

Etanercept (Enbrel):^[22,23,25,28] Etanercept is effective in reducing the signs and symptoms of RA, as well as in slowing or halting radiographic damage, when used either as monotherapy or in combination with methotrexate. Etanercept is also approved for the treatment of psoriatic arthritis and for ankylosing spondylitis as well as psoriasis. Etanercept is a fusion protein that combines two extracellular binding domains of the p75 form of the TNF receptor with the Fc portion of a human IgG1 antibody molecule. The components of the protein are entirely human, and anti-etanercept antibodies are relatively uncommon.

Mechanism of action:^[24] Etanercept binds TNF in the circulation and in the joint, preventing interaction with cell surface TNF receptors, thereby reducing TNF activity.

Dose: The most common dose currently used is 50 mg self-administered once per week by subcutaneous injection. Both prefilled syringes and an autoinjection system are available. Etanercept has a half-life of 70 hours after a 25 mg dose.

Usual time to effect: Etanercept has an onset of action of 1–4 weeks in improving signs and symptoms with additional improvements that can be seen over 3–6 months.

Side effects: As with all TNF antagonists, there is an increased risk of infection. There was an increase in upper respiratory infection symptoms in etanercept treated patients. Some patients develop positive ANA but rare cases of clinical lupus have been reported.

Etanercept and other TNF inhibitors are not recommended in patients with demyelinating disease or with congestive heart failure. Transient neutropenia or other blood dyscrasias have been reported with etanercept and the other TNF inhibitors.

Adalimumab (Humira):^[22,23,25] Adalimumab is a fully human anti-TNF monoclonal antibody with a high specificity for TNF. Like the other TNF antagonists, it is effective as monotherapy and in combination with methotrexate, at reducing signs and symptoms of RA and in slowing or halting radiographic progression of disease. It is administered by subcutaneous injection every 2 weeks but can be increased to weekly injections, if needed. Adalimumab is effective in RA, psoriatic arthritis, and ankylosing spondylitis, and Crohn's disease.

Mechanism of action:^[24] Adalimumab binds specifically to TNF and blocks its interaction with the p55 and p75 cell surface TNF receptors, thereby interfering with endogenous TNF activity. Adalimumab binds to both soluble as well as cell-bound TNF.

Dose: Adalimumab is currently available as a 40 mg dose and is given by self-administered subcutaneous (SC) injection every other week. Both prefilled syringes as well as an autoinjector system are available. Adalimumab has a half-life of approximately 10–20 days after a standard 40 mg dose.

Side effects:^[29] As with other TNF antagonists, infections are seen in clinical practice. Infections seen in clinical trials consist primarily of upper respiratory tract infections, bronchitis and urinary tract infection. Like other TNF antagonists, adalimumab is not recommended for patients with concurrent demyelinating disease or congestive heart failure. Positive ANA titers and lupus-like disease have been reported in the postmarketing period.

T-cell costimulatory blockade

Abatacept (Orencia):^[30,31] Abatacept is categorized under T-cell costimulatory blockers. These agents interfere with the interactions between antigen-presenting cells and T lymphocytes and affect early stages in the pathogenic cascade of events in RA. T lymphocytes become activated due to an unknown stimulus but likely involving the interaction between antigen presented in Class II MHC molecule on the surface of antigen presenting cells (APCs). T cells recognize antigens as foreign and if they receive a second stimulus, will become active, proliferate, traffic to inflamed sites, and secrete proinflammatory cytokines including TNF. One of the important second signals for T cell activation is mediated by the molecules CD80 and CD86 found on APCs and the CD28 molecule on the T cell surface.

Mechanism of action: Abatacept is a fusion protein that combines the extracellular domain of the molecule CTLA4 with the Fc portion of a human immunoglobulin molecule. CTLA4 has very high affinity for CD28. When abatacept binds to CD28 on the T cell surface, it prevents the second signal from being delivered, thus turning down the T cell response. Additional effects are decreasing the production of T-cell derived cytokines including TNF.

Ordinarily, full T cell activation requires 1) binding of the T cell receptor to the antigen–MHC complex on the APC and 2) a costimulatory signal provided by the binding of the T cell's CD28 protein to the B7 protein on the APC. Abatacept, which contains a high-affinity binding site for B7, works by binding to the B7 protein on APCs and by preventing them from delivering the costimulatory signal to T cells, thus preventing the full activation of T cells.

Dose: Abatacept is administered via intravenous infusion once per

month after initial doses at baseline, 2 weeks, and 4 weeks. The dose is based on body weight, with patients <60 kg receiving 500 mg, 60–100 kg receiving 750 mg, and >100 kg receiving 1000 mg. The medication is administered over a period of approximately 30 minutes to 1 hour.

Adverse effects: As with other biological DMARDs, infections are increased in patients receiving abatacept. Respiratory infections including pneumonia were more common in clinical trials in patients with underlying chronic obstructive pulmonary disease (COPD).

B cell depletion

Rituximab (Rituxan):^[32,33] B cells are important inflammatory cells with multiple functions in the immune response. They serve as antigen presenting cells, can secrete cytokines, and differentiate into antibody-forming plasma cells. Depletion of B cells has been shown to be effective in reducing signs and symptoms of RA and in slowing radiographic progression. One B-cell depleting agent, rituximab, is currently available for the treatment of RA. Rituximab (Rituxan) was originally developed to treat non-Hodgkin's lymphoma and has been used to treat this malignant condition of lymphocytes and lymph nodes for several years. Clinical studies have now demonstrated that rituximab is effective in decreasing signs and symptoms and in slowing radiographic progression in RA patients who have failed other DMARD therapies.

Mechanism of action: Rituximab is a chimeric monoclonal antibody that binds to the CD20 molecule on the B cell surface, leading to the removal of B cells from the circulation. A single course of rituximab (two infusions of 1000 mg each given 2 weeks apart) leads to a rapid and sustained depletion of B lymphocytes in the peripheral blood. This effect is sustained for 6 months to 1 year or even longer. The levels of the autoantibody rheumatoid factor decrease, but the levels of other antibodies typically remain within the normal range after the first infusion. The clinical effects are hypothesized to occur from decrease in B cell cytokines, interactions between B cells and T cells, or due to reductions in autoantibody levels.

Dose: The currently approved dose is 1000 mg administered intravenously over 3–4 hours with two doses given 2 weeks apart. The optimal time for readministration is not yet clear. Studies are ongoing to evaluate redosing schedules.

Adverse effects: Infusion reactions are seen in patients who receive rituximab infusions. These may include hives, itching, swelling, difficulty breathing, fever, chills, and changes in blood pressure. These are usually mild and respond to slowing the infusion rate or additional medication (such as antihistamines) but may be severe. These reactions were the most common with the first infusion. As with other immunomodulatory therapies, infections may be increased in patients who receive rituximab.

The use of monoclonal antibodies in RA has been valuable in assessing the roles of various inflammatory mediators and cell-bound molecules in disease pathogenesis. Nevertheless, monoclonal antibodies will be judged ultimately by their use as a therapy for RA in routine clinical practice. The ideal treatment of RA should be safe, produce sustained disease remission and stop radiological damage after a brief course of treatment. If repeated treatments are necessary, they must be safe and economical to use in the long term. It is against these criteria that new treatments for RA, including mAb, should and will be assessed.

Newer TNF- α blockers

Certolizumab pegol (Cimzia[®]):^[34-36] Certolizumab pegol (Cimzia) is the first PEGylated anti-TNF- α monoclonal antibody that has a high affinity for human TNF- α and selectively targets TNF- α in inflamed tissue. Excess TNF- α production has been implicated in a wide variety of diseases, including Crohn's disease and RA. On April 22, 2008, USFDA approved the drug for use in the US on for the treatment of Crohn's disease in people who did not respond sufficiently or adequately to standard therapy.

Mechanism of action:^[37] Certolizumab pegol is a monoclonal antibody directed against TNF- α . More precisely, it is a PEGylated Fab' fragment of a humanized TNF inhibitor monoclonal antibody. Cimzia is a recombinant, humanized antibody Fab' fragment, with specificity for human TNF- α , conjugated to an approximately 40 kDa polyethylene glycol (PEG2MAL40K). TNF- α is a key pro-inflammatory cytokine with a central role in inflammatory processes. Certolizumab pegol selectively neutralizes TNF- α , but does not neutralize lymphotoxin a (TNF- β). Certolizumab pegol was shown to neutralize membrane-associated and soluble human TNF α in a dose-dependent manner. Incubation of monocytes with certolizumab pegol resulted in a dose-dependent inhibition of LPS-induced TNF- α and IL-1 β production in human monocytes.

Side effects:^[38] Adverse events associated with the use of Cimzia may include upper respiratory tract infection, headache, hypertension, nasopharyngitis, back pain, pyrexia, pharyngitis, rash, acute bronchitis, fatigue.

Clinical trials:^[39-42] Positive results have been obtained in two phase III trials (PRECISE 1 and 2) of certolizumab pegol versus placebo in moderate to severe active Crohn's disease. In addition, data from both the trials suggest that it is well-tolerated. As yet, its efficacy has not been directly compared to other anti-TNF- α agents. Preliminary results of the RAPID 1 and a 2 phase III studies were also reportedly positive.

Golimumab (Simponi):^[43] Golimumab is a human monoclonal antibody which is marketed under the brand name Simponi. Golimumab targets TNF- α , a pro-inflammatory molecule and hence is a TNF inhibitor.

Golimumab was developed by Centocor, Pennsylvania, USA Horsham and is approved in Canada and the United States as a once monthly subcutaneous treatment for adults with moderately to severely active RA, active psoriatic arthritis, and active ankylosing spondylitis.

Golimumab is similar to infliximab, except that it has been engineered to be fully human and is given as a subcutaneous injection.

Drugs used in cardiovascular system

Abciximab:^[44] Abciximab is indicated for use in individuals undergoing percutaneous coronary intervention (angioplasty with or without stent placement). The use of abciximab in this setting is associated with a decreased incidence of ischemic complications due to the procedure and a decreased need for repeated coronary artery revascularization in the first month following the procedure.

Pharmacokinetics: Abciximab has a plasma half-life of about 10 minutes, with a second phase half-life of about 30 minutes. However, its effects on platelet function can be seen for up to 48 hours after the infusion has been terminated, and low levels of glycoprotein IIb/IIIa receptor blockade are present for up to 15 days after the

infusion is terminated.

Side effects: Many of the side effects of abciximab are due to its anti-platelet effects. These include an increased risk of bleeding. The most common type of bleeding due to abciximab is gastrointestinal hemorrhage. Thrombocytopenia is a rare but known serious risk. Abciximab-induced thrombocytopenia can typically be treated with transfusion of platelets.

Drugs used in transplant rejection

Basiliximab:^[45] Basiliximab (Simulect) is a chimeric mouse-human monoclonal antibody to the IL-2R α receptor of T cells. It is used to prevent rejection in organ transplantation, especially in kidney transplants. It is a Novartis Pharmaceuticals, Cambridge, USA product and was approved by FDA in 1998.

Dose: It is given in two doses, the first within 2 hours of the start of the transplant operation and the second 4 days after the transplant. These saturate the receptors and prevent T cell activation and thus prevent formation of antibodies against the transplant.

Like daclizumab (a similar drug), basiliximab reduces the incidence and severity of acute rejection in kidney transplantation without increasing the incidence of opportunistic infections. Adalimumab, Eculizumab, Efalizumab are also used in the treatment of transplant rejection. In UK, the National Institute for Health and Clinical Excellence has recommended its use be considered for all kidney transplant recipients.

Conclusions

Monoclonal antibodies drive the development of multibillion dollar biotechnology industry. Many of the pharmaceutical companies have entered monoclonal antibodies sector, attracted by quicker and less costly development, higher success rates, premium pricing and a potentially reduced threat from generics. The outlook for monoclonal antibody therapeutics is healthy. The ongoing success of existing products, combined with a bulging pipeline of new products awaiting approval and limited generics erosion, point toward robust growth in this segment.

At present, monoclonal antibodies are administered as IV infusions. Clearly, close medical and nursing supervision is required, which increases the cost of treatment and provides a significant practical burden. However, the dose of antibody required for treatment is small; perhaps antibody could be administered SC or IM, although such routes of administration can theoretically increase the likelihood of the development of anti-globulin antibodies.

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