CHAPTER

34

Monoclonal Antibodies: What Clinicians Should Know

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INTRODUCTION

It is the duty of the physician to keep abreast of new developments and be in position to offer the most optimal treatment to the patient. Monoclonal antibodies are now becoming available to treat malignant, autoimmune and inflammatory disorders and even some infectious diseases.

HISTORY AND MANUFACTURE OF MONOCLONAL ANTIBODIES

Kohler and Milstein in 1975 devised a technique for which they were awarded the Nobel prize in 1984. They combined the unlimited growth potential of myeloma cells with the antibody specificity of normal B cells. For this they used the following steps:

First, a mouse was immunized by injections of a specific antigen.

Next, splenectomy was carried out and the B cells fused to myeloma cells using polyethylene glycol, yielding fused hybridoma cells.

Myeloma cells that have lost the ability to synthesize HGPRT cannot survive in a special medium called HAT (hypoxanthine, aminopterin and thymidine). In this medium the unfused spleen cells die out, myeloma cells cannot survive but the hybridoma cells can survive and grow indefinitely.

Now individual cells from the cell culture can be sub-cultured and the supernatant tested for desired antibodies. This is the most tedious labour intensive part of the process.

Selected cultures can be grown indefinitely in vitro or in mice, to yield desired antibodies.

Mouse antibodies are seen as foreign antigens by patients' immune system, and antibodies can be produced against them. To reduce this problem, chimeric antibodies can be produced that are part human; or humanized antibodies; using recombinant technology. These can be grown in mammalian cell cultures.Transgenic mice may be used in the future for production of monoclonal antibodies.

Applications of monoclonal antibodies are increasing every day. A partial list follows:

AUTOIMMMUNE DISEASES

Adalimumab

Recombinant Human Anti-TNF-α antibody. Blocks the binding of TNF-α to cells, destroys cells which have this inflammatory mediator bound to the surface, hence reduces inflammation.

Available as 40 mg/ 0.8 ml prefilled syringe.

Used for rheumatoid arthritis, psoariasis with or without arthritis, ankylosing spondylitis, Crohn's disease and ulcerative colitis, uveitis and Behcet's disease.

Typical dosing is 40 mg SC once every two weeks; some conditions need a higher starting dose.

Common side effects include local pain, URTI and sinusitis, rash, headache, elevated CPK.

Vedolizumab

Recombinant humanized antibody, binds to an integrin, inhibits migration of memory T lymphocytes across the endothelium into inflamed gut.

300 mg vial.

Ulcerative colitis and Crohn's disease.

300 mg IV at 0, 2, 6 weeks. Maintenance 300 mg every 8 weeks.

allergy; incidence 5% overall.

Golimumab

Human Anti- TNF-α, blocks inflammatory activity.

50 & 100 mg/ml.

Used for RA and psoariatic arthritis, ankylosing spondylitis, ulcerative colitis.

Usual dose 50 mg / month SC.

Infections, rash, leukopenia, immune reactions in the skin and lungs.

Infliximab

Recombinant humanized Anti TNF-α action.

100 mg/ vial.

Used for RA, AS, psoariasis with / without arthritis.

Dose 5 mg/kg IV at 0, 2, 6 weeks and every 6 weeks afterwards.

Increased risk of infections, including TB, invasive fungi, legionella, listeria, viruses.

Lymphomas have been reported.

Secukinumab

Human Neutralizes interleukin -17A.

Available as 150 mg vial.

Used for treatment of psoariasis and ankylosing spondylitis.

Dose 300 mg/ weekly SC for 5 weeks then 300 mg/ month.

As many as 30% patients may develop infections during the treatment. TB must be ruled out beforehand. Live vaccines cannot be given during treatment.

Alefacept
A recombinant dimeric fusion protein that inhibits T cell activation.

Available as vials of 7.5 and 15 mg.

Used to treat psoariasis.

Dosing is 15mg/ week IM for 12 weeks.

Local reactions and lymphopenia may occur.

Ustekinumab
Human; antagonizes IL-12 and IL-23.

90 mg/ml; SC injection.

Psoariasis with or without arthritis. Under study for type 1 DM with preserved beta cell function and for biliary cirrhosis.

Hypersensitivity reactions, severe infections and development of malignancy are possible major adverse effects, apart from minor reactions.

Usual dose 45 mg SC, then repeat at 4 weeks and every 12 weeks later.

TRANSPLANT REJECTION

Basiliximab
Interleukin-2 receptor antagonist.

10/ 20 mg IV injections are available.

Used along with steroids and cyclosporine in renal transplant for preventing rejection.

INFECTIOUS DISEASES

Bezlotoxumab
Fully human; Binds C. Difficile toxin and neutralizes it, does not allow binding to human colonic cells.

FDA approval pending.

Raxibacumab
Recombinant human; against bacillus Anthracis.

IV formulation 50 mg/ml.

Treatment of inhalational Anthrax.

40 mg/kg IV single dose over 2.5 hrs.

Requires dose of diphenhydramine as premedication.

Zmapp
Combination of 3 monoclonal antibodies against Ebola virus surface glycoprotein GP.

Was used in the recent Ebola epidemic in Africa.

NEUROLOGY

Daclizumab
Humanized; Binds IL-2 receptor subunits, which are expressed on T cells. So inhibits abnormally activated T cells in multiple sclerosis.

150 mg/ ml in a single dose prefilled syringe.

For multiple sclerosis.

150 mg SC once a month.

Need to rule out existing and developing autoimmune hepatic damage or tuberculosis. Live vaccine contraindicated during therapy. Immune mediated skin disease.

Natalizumab
Recombinant human, binds to integrin subunits, prevents leukocyte-endothelial adhesion

300 mg/15 ml.

Multiple sclerosis; Crohn's disease.

300 mg IV over 1 hr, every month.

Risk of PML, IRIS in patients of PML, allergy, HSV/VZV encephalitis, hepatic injury can occur.

MULTIPLE APPLICATIONS

Rituximab
Humanized, anti CD-20, cytolytic.

10 mg/ml.

NHL, CLL, RA, Wegener granulomatosis, microscopic polyangiitis, ITP, pemphigus vulgaris.

Usual dose 375 mg/m^2 IV then maintenance.

Fatal infusion reactions can occur. Mucocutaneous reactions, PML, hepatitis B reactivation, arrhythmia, tumour lysis can occur.

MALIGNANT DISEASES

Ofatumumab
Human, anti CD-20, inhibits B cell activation.

100 mg/ 5 ml and 1000 mg/ 50 ml vials.

Used for CLL.

Allergy, Hep B activation, PML can occur.

Ibritumomab tiuxetan, obinutuzumab
Both these are also anti-CD 20 antibodies for use in CLL.

Alemtuzumab
Recombinant, anti CD-52, causes lymphocyte lysis.

CLL, multiple sclerosis. Can be used for kidney transplant rejection.

Bevacizumab
Recombinant humanized, blocks angiogenic molecule VGEF.

25 mg/ ml.

Metastatic colorectal cancer, non- small cell lung cancer, breast cancer, renal cell cancer, cervical, ovarian, fallopian tube cancer.

GI perforation, wound dehiscence, hemorrhage, thrombosis are possible side effects.

Brentuximab
CD-30 directed antibody-drug conjugate.

50 mg/ vial.

Hodgkin's lymphoma, anaplastic large cell lymphoma.

1.8 mg/kg IV every 3 weeks.

PML, pulmonary toxicity, neuropathy, SJS, anaphylaxis, hepatic failure, GI perforation.

Denosumab
Binds to RANKL and inhibits its binding to RANKL receptors, thus inhibits osteoclast formation.

60 or 70 mg/ml vials.

Hypercalcemia of malignancy, prevention of fractures in patients with bone metastases, osteoporosis, giant cell tumor.

Allergy, hypocalcemia, serious infections need to be watched for. Osteonecrosis of jaw may occur. Bone pain, pancreatitis reported.

60 mg SC once a month.

Cetuximab

Recombinant humanized, binds EGF receptors.

2 mg/ml.

Colorectal and head and neck cancer.

Infusion reactions, cardiac arrest, muco-cutaneous reactions.

400 mg/m^2 IV then maintenance.

Panitumumab works by same mechanism as above.

Daratumumab

Anti CD-38, expressed on myeloma cells.

100 mg/5 ml, 400 mg/ 20 ml.

Multiple myeloma, diffuse large B cell lymphoma.

Infusion reactions in 50%.

Dinutuximab

Chimeric anti-gd-2.

17.5 mg/ ml.

Pediatric neuroblastoma.

Infusion reactions, neuropathy, marrow suppression, infection.

Dinutuximab works by same mechanism.

Elotuzumab

Humanized, targets SLAMF7; activates natural killer cells to destroy myeloma cells

300 mg/vial.

Used with dexamethasone and linelidomide in myeloma therapy.

Trastuzumab

Anti HER-2.

440 mg/vial.

Breast, gastric, pancreatic cancer.

4 mg/kg IV then weekly 2 mg/kg.

Cardiac failure, infusion reactions, pulmonary toxicity, fetal toxicity.

Pertuzumab also works by same mechanism.

Siltuximab

Binds IL-6.

100 mg/ vial.

Castleman's disease.

1 mg/kg IV every 3 weeks.

Anaphylaxis, infections, teratogenicity, GI perforation.

Ipilimumab

T cell antibody.

50 mg/ 10 ml, 200 mg/ 40 ml.

Malignant melanoma.

3 mg/kg IV every 3 weeks. Max 4 doses.

Immune reactions in any organ.

Pembrolizumab

Anti- programmed cell death- 1 protein(PD- 1)

50 mg/ vial.

Melanoma, non small cell lung cancer.

2 mg/kg IV every 3 weeks.

Anaphylactic reactions and immune reactions in various organs.

Nivolumab works by same mechanism as above.

HEMATOLOGY

Eculizumab

Blocks complement protein C5.

10 mg/ml.

In atypical HUS, inhibits complement mediated thrombotic microangiopathy. Reduces hemolysis in PNH.

Being studied for myasthenia, neuromyelitis optica and dermatomyositis. Minor reactions common, increased risk of meningococcal infection.

CARDIOVASCULAR

Evolocumab

Antibody to PCSK9.

420 mg every 4 weeks.

Hypercholesterolemia.

Abciximab

Antiplatelet GpIIb/IIIa inhibitor.

Supplied as 2 mg/ml; given 0.25 mg/kg bolus before PCI, then infusion.

For PCI, NSTEMI, STEMI.

Bleeding, hypotension, nausea, allergy.

It is mind-boggling to imagine what novel applications will emerge for this technology in the future.

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