



DRUG ALERT

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MONOCLONAL ANTIBODIES

Humans (and mice) have the ability to make antibodies which can recognize (by binding to) virtually any antigenic determinant (epitope) and discriminate between similar epitopes. This provides the basis for protection against disease and organisms, and it makes antibodies attractive candidates to target other types of molecules found in the body, such as receptors or other proteins present on the surface of normal cells and molecules present uniquely on the surface of cancer cells.

Thus the remarkable specificity of antibodies makes them promising agents for human therapy. For example:

- ▶ Make an antibody that will bind only to the cancer cells in a patient.
- ▶ Coupling of a cytotoxic agent or a strong radioactive isotope to that antibody so that it can seek out and destroy the cancer cells and not normal cells.

Monoclonal antibodies are produced by B-cells that have been challenged with an antigen. Each B-cell produces only one kind of antibody which is fused to myeloma tumor cells (Myeloma is a B-cell cancer). These fused hybrid cells called hybridomas will multiply rapidly and indefinitely and will produce large amount of antibodies. Monoclonal antibodies can be produced in cell cultures or in animals.

Monoclonal antibodies are classified and named based on their derivation. Murine monoclonal antibodies have the suffix “- *momab*”, are cleared quickly from the body and have a greater chance of inducing a HAMA reaction (human anti-mouse antibody). Chimeric antibodies are a human-mouse antibody mixture; they possess the suffix “- *imab*” and are more efficient and effective at destroying cells via CDC (Complement-dependent cytotoxicity) and ADCC (antibody dependent cell-mediated cytotoxicity). Chimeric antibodies circulate longer in the human body and are less likely to invoke a HAMA reaction. Humanized monoclonal antibodies possess the suffix “- *umab*” and are not likely to invoke a HAMA reaction.

Clinical uses:

- a) Imaging of tumors using radioisotope - labeled monoclonal antibodies.

- b) Selectively purging bone marrow of cancer cells.
- c) Treatment of specific conditions like rheumatoid arthritis, Crohn’s disease, allergic asthma etc.
- d) Treatment of other conditions like transplant rejection, infections etc.

Monoclonal antibody therapy is based on the ability to target markers and bind to cell membrane antigens with great specificity. Most of the time the enhanced specificity demonstrated toward tumor antigens allows protection of normal cells unlike conventional therapy. There are several mechanisms by which monoclonal antibodies destroy or prevent further replication of malignant cells. Some monoclonal antibodies utilize tumor immunology and components of the host natural defense mechanism to exert their desired effect. For example, monoclonal antibodies can utilize tumor effector cells to promote tumor cell lysis or they have the ability to directly modulate tumor function. Conjugated monoclonal antibodies can be used as carriers of toxic therapy, such as radionuclides, cytotoxic drugs or cell clones to target specific cells. They are also being employed to create tumor vaccines by stimulating a host antibody reaction causing the production of anti-idiotypic antibodies. In the last five years selected monoclonal antibodies have become a standard care for treatment of certain malignancies. They are also used in the treatment of other disease conditions like rheumatoid arthritis, Crohn’s disease, allergic asthma etc.

Side effects:

Monoclonal antibodies are given intravenously. Compared with side effects of standard chemotherapy, the side effects of naked MAbs are usually relatively mild and are often related to an “allergic” reaction. If they do occur, it is often while the drug is first being infused. Possible side effects include fever, chills, weakness, headache, nausea, vomiting, diarrhea, hypotension and rashes.

Some MAbs can also affect the bone marrow in a way similar to what most chemotherapy drugs can do. This can result in pancytopenia, which can lead to an increased risk of bleeding and infection in some people.

Adverse effects seen with some of the MAbs is given in Table 1

Table 1: Some of the adverse effects reported for the individual MAbs.

Name of the drug	Adverse effects
Rituximab	Tumor lysis syndrome, arrhythmias, and pulmonary dysfunction
Alemtuzumab	Immunosuppression, increased risk of infection
Gemtuzumab ozogamicin	Hepatotoxicity, bone marrow suppression
Trastuzumab	Pulmonary or cardiac toxicity
Infliximab	Active tuberculosis
Muromonab	Cytokine release syndrome
Bevacizumab	Hypertension, hemorrhage, gastrointestinal perforation
Cetuximab	Rashes, infusion reaction
¹³¹ I- tositumomab	Secondary leukemias
⁹⁰ Y-ibritumomab tiuxetan	Secondary leukemias

Some of the uses/indications of MAbs are as follows:

Cancer:

- ▶ Rituximab (Rituxan) - approved in 1997, used in the treatment of relapsed/ refractory low grade B-cell non-Hodgkin lymphoma
- ▶ Trastuzumab (Herceptin) - approved in 1998, used in the treatment of breast cancer that over expresses the HER2 protein.
- ▶ Alemtuzumab (Campath-1H) - approved in 2001 - indicated in T-cell prolymphocytic leukaemia, refractory B-cell CLL.
- ▶ Cetuximab (Erbix) - (epidermal growth factor receptor inhibitor) approved in 2004 for treatment of colon cancer and lung cancer.
- ▶ Bevacizumab (Avastin) (Vascular endothelial growth factor inhibitor) approved in 2004 used for treatment of colorectal cancer.
- ▶ Vitaxin - angiogenesis inhibitor used in treatment of solid tumors.

Conjugated MAbs used in Cancer:

- ▶ Gemtuzumab ozogamicin (Mylotarg) conjugated with calicheamicin used in CD 33 positive AML.
- ▶ ⁹⁰Y-Ibritumomab tiuxetan (Zevalin) - MAb conjugated with either Indium-111 or Yttrium-90 used in the treatment of B-cell lymphoma, targets CD20 molecule.
- ▶ ¹³¹I-Tositumomab (Bexxar) a conjugate of a monoclonal antibody against CD 20 and radioactive iodine-131 used in the treatment of B-cell lymphoma.

MAbs used in suppressing the immune system:

- ▶ Muromonab - CD3 (OKT3) used to prevent acute rejection of organ eg. kidney transplant.

- ▶ Daclizumab (Zenapax) used to prevent acute rejection of kidney transplant, also used in T-cell lymphoma.
- ▶ Infliximab (Remicade) - used in rheumatoid arthritis.
- ▶ Omalizumab (xolair) - used in allergic asthma.

Cardiovascular disease:

- ▶ Abciximab - used in unstable angina, inhibits clumping of platelets.

Viral infections:

- ▶ Palivizumab used in RSV prophylaxis and bronchopulmonary dysplasia in infants/ young children.

MAbs currently approved in India:

- *Rituximab* – antineoplastic
- *Trastuzumab* – antineoplastic
- *Daclizumab* – immunosuppressive

Key points

1. MAbs are specific antibodies derived from single B-cell clone. They act by antibody - dependent cellular cytotoxicity (ADCC), complement - dependent cytotoxicity (CDC) and induction of apoptosis.
2. Most common adverse effects are infusion related reactions, myelosuppression and hypersensitivity reactions.
3. MAbs are used in the treatment of variety of conditions like cancer, rheumatoid arthritis, RSV prophylaxis, allergic asthma etc.

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