Monoclonal Antibodies

Monoclonal antibodies are increasingly relied upon as a treatment option for numerous disease states. The goals of this self-study module are to help you understand monoclonal antibodies (mAB) — what they are and how they are made — and provide some examples of how they are used in the healthcare setting.

Before considering monoclonal antibodies, it is helpful to review the role of antibodies in general. An antibody is developed by the immune system specifically for an antigen. An antibody is only effective against that antigen for which it was formed. The common cold provides an example of this concept. A cold is caused by a specific virus. The virus, then, is the antigen. When the antigen enters the body, the immune system takes steps to build an antibody against that specific cold virus. If a person gets a cold from another cold virus, the antibodies already made will not be effective against the new virus. There is also a “learned response” with antibodies. If those same antigens re-present, the antibodies will quickly reactivate and swarm, destroying the viral antigen before it can cause a second bout of that specific cold. Thus, once you have a cold from a specific virus, you cannot be infected with that specific virus again. If you are re-exposed, the antibodies will quickly get to work. Unfortunately, there are multitudes of different cold viruses, so you’ll still get plenty of colds, just not with the same virus twice.

Monoclonal antibodies are groups of cells (antibodies) that are produced from a single ancestral cell by repeated cellular replication. Through a multi-step process, the original antibody is replicated, or clones itself, over and over. Referring to the illustration above — if a human substance is injected into a mouse, for example, that substance, or antigen, is foreign to the mouse. The mouse’s immune system will activate, ultimately producing B cells and the antibody that binds to that specific antigen. We now have antibodies against the human substance that was injected.

To produce monoclonal antibodies, B cells are removed from the spleen of the mouse and then fused with myeloma tumor cells that can grow indefinitely in culture. Myeloma is a rapidly growing B-cell cancer. The fused hybrid cells are called hybridomas and they will multiply rapidly and indefinitely, ultimately producing large amounts of antibodies. The strongest of the antibodies are cloned, ultimately creating a line of identical antibodies, specific to a particular antigen target.

Monoclonal Antibodies as Clinical Therapy

Monoclonal antibodies work in different ways, depending on the disease being treated and the biology of the target. A therapeutic monoclonal antibody may bind to and neutralize the normal function of a target. For example, a monoclonal...
antibody that blocks the activity of the protein needed for the survival of a cancer cell causes the cell's death.

Another therapeutic monoclonal antibody may bind to and activate the normal function of a target. For example, a monoclonal antibody can bind to a protein on a cell and trigger an apoptosis signal, i.e., the signal for the cell to self-destruct.

And thirdly, if a monoclonal antibody binds to a target expressed only on diseased tissue, the treatment, e.g., chemotherapy, can be directed to the tumor, reducing harm to healthy tissue.

Diseases especially amenable to antibody-based treatments today include cancer, immune dysregulation or autoimmune diseases, and infection. There are many examples of monoclonal antibodies for these disease states, each with its own unique method of action. It is beyond the scope of one continuing education program to detail each available mAB. This educational program, then, will overview several examples in order for the reader to appreciate the different mechanisms of action and potential adverse effects.

### Cancer

The table below lists the current FDA-approved mABs for cancer therapies. Note: the FDA recently deleted breast cancer from its approved list for Avastin, stating a lack of proven effectiveness.

When a monoclonal antibody attaches to a cancer cell, it can:

**Make the cancer cell more visible to the immune system.** The immune system attacks foreign invaders in the body, but it doesn't always recognize cancer cells as enemies. A monoclonal antibody can be directed to attach to certain parts of a cancer cell. In this way, the antibody marks the cancer cell and makes it easier for the immune system to find and then destroy it.

The mAB rituximab (Rituxan) attaches to a specific protein that is only found on B cells, which are cells that can cause certain types of lymphomas. When rituximab attaches to the protein on the B cells, it makes the cells more visible to the immune system, which can then attack. Rituximab lowers the number of B cells, including healthy B cells, but the body produces new healthy B cells to replace these. The cancerous B cells are less likely to recur.

Rituximab is also used in combination with methotrexate to treat rheumatoid arthritis. Rituximab can cause serious side effects, some of which can be life-threatening, including: progressive multifocal leukoencephalopathy (PML), infusion reactions, tumorlysis syndrome (TLS), and severe skin reactions. Other serious and life-threatening side effects with Rituxan (Rituxin) include: hepatitis B virus reactivation, heart problems, infections, and stomach and bowel problems. Common side effects during Rituxan (Rituxin) infusions include: fever, headache, chills and shakes, nausea, itching, hives, cough, sneezing, and throat irritation or tightness.

Rituxan is typically administered weekly for 4 to 8 weeks. In the treatment of rheumatoid arthritis, a patient may receive only two injections of this medicine, with 2 weeks between treatments.

**Block growth signals.** Chemicals called growth factors attach to receptors on the surface of our cells, both normal cells and cancer cells, signaling to the cells to grow. Certain cancer cells make extra copies of the growth factor receptor. This makes them grow faster than the normal cells. Monoclonal antibodies can block these receptors and prevent the growth signal from getting through.

Cetuximab (Erbitux) is a monoclonal antibody used to treat colon and head and neck cancers. This mAB attaches to the receptors on cancer cells that accept the growth signal. Blocking this signal from reaching its target on the cancer cells may slow or stop the growth of the cancer.

**Deliver radiation to cancer cells.** By combining a radioactive particle with a monoclonal antibody, physicians can deliver radiation directly to the cancer cells, reducing damage to surrounding healthy cells. Radiation-linked monoclonal antibodies deliver a low level of radiation over a longer period of time, which appears to be as effective as the more conventional high-dose external beam radiation.

---

<table>
<thead>
<tr>
<th>Name of drug</th>
<th>Type of cancer treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alemtuzumab (Campath)</td>
<td>Chronic lymphocytic leukemia</td>
</tr>
<tr>
<td>Bevacizumab (Avastin)</td>
<td>Colon, lung cancers</td>
</tr>
<tr>
<td>Cetuximab (Erbitux)</td>
<td>Colon, head and neck cancers</td>
</tr>
<tr>
<td>Gemtuzumab (Mylotarg)</td>
<td>Acute myelogenous leukemia</td>
</tr>
<tr>
<td>Ibritumomab (Zevalin)</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Panitumumab (Vectibix)</td>
<td>Colon cancer</td>
</tr>
<tr>
<td>Rituximab (Rituxan)</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Tositumomab (Bexxar)</td>
<td>Non-Hodgkin's lymphoma</td>
</tr>
<tr>
<td>Trastuzumab (Herceptin)</td>
<td>Breast cancer</td>
</tr>
</tbody>
</table>

Table 2
Allergic reactions, such as hives or nausea, can occur and, very rarely, lead to death. Pre-meds may be needed to prevent or minimize infusion reactions.

Severe hypersensitivity reactions can occur and, very rarely, lead to death. Pre-meds may be needed to prevent or minimize infusion reactions.

Rare but more serious side effects of monoclonal antibody therapy include:

- Moderate acute infusion reactions in 5%–10% of patients. Reactions may occur with any dose of therapy; however, they are more common with the first two doses. Severe hypersensitivity reactions can occur and, very rarely, lead to death. Pre-meds may be needed to prevent or minimize infusion reactions.
- Severe decreased levels of red blood cells, white blood cells and platelets.
- Cardiac complications, including heart failure or infarct, which may be caused by certain monoclonal antibodies.

Since monoclonal antibodies attack only the molecule to which they are targeted, administration typically results in no, or greatly diminished, side effects. Some of the more common side effects of monoclonal antibodies include:

- Allergic reactions, such as hives or itching
- Flu-like symptoms, including chills, fatigue, fever, and muscle aches and pains
- Nausea
- Diarrhea
- Skin rashes

Because of the risk of PML, Tysabri can only be prescribed, distributed and infused by prescribers, infusion centers, and pharmacies with infusion centers that are registered in the Tysabri TOUCH™ program. Requirements of this program include proof of patient education and consent, and patient evaluation at three and six months and then every six months after their first infusion. Patients must also be enrolled in the program and meet all of the necessary conditions of the program.

**Autoimmune Disease**

Monoclonal antibodies are used to treat many autoimmune diseases. They bind to and inhibit tumor necrosis factor (TNF).

Natalizumab (Tysabri®) is one example. Tysabri is approved as a single therapy for patients with relapsing remitting multiple sclerosis (RRMS) to delay disease progression and reduce the rate of relapse. It is also approved for treatment of Crohn’s disease, typically after other drugs have been tried.

Tysabri works by binding to and blocking the effects of white blood cells. It prevents the white cells from entering areas where they would cause inflammation and damage — the brain and spinal cord in MS, and the intestine in Crohn’s disease.

Tysabri does present with risk for several potentially serious adverse effects. Less than 1% of the patients will develop hypersensitivity, in which case the Tysabri must be discontinued. There is a slight risk of liver damage and, as with all mABs, a risk of infection, often opportunistic, due to the immunosuppressive effects.

Rare cases of progressive multifocal leukoencephalopathy (PML), a disease of the brain that typically leads to permanent disability or death, were identified. The risk was found to be higher in patients also taking Tysabri in combination with other immunomodulators, such as interferons or immunosuppressant medications. PML did not occur in patients treated with Tysabri alone and the drug is approved as monotherapy.

Bevacizumab (Avastin) starves the tumor of what it needs to grow and spread. Avastin works by blocking the protein called vascular endothelial growth factor (VEGF). VEGF, important for the formation of blood vessels, is produced by normal cells and overproduced by cancer cells. By blocking VEGF, Avastin essentially starves the malignant tumor.

**Transplantation**

Monoclonal antibodies are used in transplantation to eliminate or block the function of the cells necessary for the rejection response.

Basiliximab (Simulect®) is a monoclonal antibody directed to a specific site on a T cell. It saturates the receptors and prevents T cells from replicating and also from activating antibodies that would bind to the transplanted organ and fuel a rejection response. Simulect has been shown to reduce the incidence and severity of acute rejection in kidney transplantation. Also of note — because this mAB is so specific in terms of where on the T cell it works, it does not increase the incidence of opportunistic infections as most mABs do.

Simulect is given in two doses, the first within 2 hours of the start of the transplant surgery, the second at 4 days post-transplant. It is administered either as a bolus injection or diluted and given by IV over 20-30 minutes.

**Other Indications**

Other examples of mABs are listed in Table 3 (located on the back cover).
Sores, including of the oral mucosal lining, and skin rashes, both of which can lead to serious infections.

Bleeding; reports indicate that this has been caused by monoclonal antibodies designed to block VEGF.

Other warnings may be product-specific, such as: fatal infusion reactions (muromonab, infliximab); cardiomyopathy (trastuzumab); myelosuppression (alemtuzumab); development of gastrointestinal perforation and wound dehiscence, in some instances resulting in fatality (rituximab, bevacizumab); and progressive multifocal leukoencephalopathy (natalizumab).

Many mABs have black box warnings. Prior to administration, the manufacturer information should be reviewed for the specific mAB prescribed.

All mABs released thus far have product warnings related to severe hypersensitivity reactions, opportunistic infections, and the re-activation of tuberculosis (TB) or hepatitis B.

**Administration**

Specific administration protocols may differ depending on drug, disease and patient factors. However, it is typically recommended that prior to the first home dose, patients receive at least 2 doses of any mAB in a monitored setting and experience no severe infusion or adverse reaction. Patients should be at least 5 years old and have signed an appropriate informed consent (drug-specific or general mAB consent if no drug-specific informed consent is available). Each patient’s current TB and hepatitis B status should be known and documented.

Other administrative protocols include:

- Obtain and review any pre-medication orders.
- Obtain acute infusion reaction orders based on site of administration.
- Since most mAB infusions are given monthly, peripheral lines tend to be used unless otherwise specified in the manufacturer information, or if the patient has a pre-existing central access.
- Vital signs should be taken prior to and at least every 30 minutes during the infusion, and for a minimum of 30 minutes post-infusion based on the patient’s clinical tolerance.
- Patients should be monitored for infusion reaction-type side effects at least every 30 minutes during infusion and for a minimum of 30 minutes post-infusion, again based on the patient’s clinical tolerance.

**mAB**

<table>
<thead>
<tr>
<th>mAB</th>
<th>Clinical Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Abciximab (ReoPro)</strong></td>
<td>Developed to inhibit platelet aggregation in the blood. It is used to treat some forms of cardiovascular disease.</td>
</tr>
<tr>
<td><strong>Palivizumab (Synagis)</strong></td>
<td>Provides replacement antibodies specific to RSV. Full-term babies obtain virus-fighting antibodies from their mothers during pregnancy. Babies born prematurely often do not get enough of these antibodies before birth.</td>
</tr>
<tr>
<td><strong>Ranibizumab (Lucentis)</strong></td>
<td>Treats wet macular degeneration (WMD). WMD is caused by the abnormal growth of blood vessels in the retina. Lucentis binds to and prevents VEGF from stimulating new blood vessel growth and blood vessel leakage. It is injected directly into the affected eye monthly.</td>
</tr>
<tr>
<td><strong>Eculizumab (Solaris)</strong></td>
<td>An orphan drug used for the treatment of paroxysmal nocturnal hemoglobinuria (PNH), a very rare blood disorder in which red blood cells develop abnormally. Naturally occurring proteins designed to destroy bacteria and other organisms break these cells down. Solaris blocks complement (part of the immune system) needed for that breakdown.</td>
</tr>
<tr>
<td><strong>Omalizumab (Xolair)</strong></td>
<td>Captures IgE, which is produced in response to certain allergens, to help stop asthma attacks and symptoms before they start.</td>
</tr>
</tbody>
</table>

**Table 3**

- Infusions should be done per the manufacturer guidelines. Most mAB infusions are initiated at a slow rate and then titrated upward based on patient tolerance.

- The majority of reactions are not allergic and respond quickly to a reduction in the infusion rate and administration of diphenhydramine and acetaminophen as needed.

- For any severe reaction, the infusion must be discontinued.

**References**


Monoclonal Antibodies

LEARNING GOAL
To understand what monoclonal antibodies are and how they work as therapy options for numerous disease states.

LEARNING OBJECTIVES
After reviewing this publication, each participant should be able to:
1. Define monoclonal antibodies.
2. Describe the production of monoclonal antibodies.
3. Explain the use of monoclonal antibodies in the clinical setting.

SELF-ASSESSMENT QUESTIONS
Please circle the correct answer for each question. The passing score for this test is 100%.

3. Diseases especially amenable to antibody-based treatments today include:
   a. Cancer.
   b. Autoimmune diseases.
   c. Infection.
   d. All of the above.
   e. A and B only.

4. Which of the following statements is FALSE? Hybridoma cells:
   a. Are a fusion of antibody with myeloma tumor cells.
   b. Multiply rapidly for a defined period of time.
   c. Produce clones of the original antibody.
   d. All of the above.
   e. A and C only.

5. Which of the following statements is FALSE? In cancer, a monoclonal antibody may:
   a. Attach to a cancer cell so that the immune system is no longer able to recognize it.
   b. Block cell receptors for growth factor.
   c. Be combined with a radioactive particle.
   d. Block angiogenesis.
   e. A and B only.

6. Monoclonal antibodies minimize the risk of opportunistic infection(s).
   a. True.
   b. False.
7. Monoclonal antibodies are used in transplantation to eliminate or block the function of the cells necessary for the rejection response.
   a. True.
   b. False.

8. Which of the following statements is FALSE? Adverse reactions with monoclonal antibodies:
   a. Tend to be diminished because the target is so specific.
   b. Vary between specific monoclonal antibodies.
   c. Often (>20% of the time) include serious hypersensitivity reactions.
   d. May require pre-medication(s).
   e. Are typically dose-related.

9. All of the following are true EXCEPT: Monoclonal antibody administration:
   a. Is based on manufacturer recommendations specific to each product.
   b. Must be done via a central line.
   c. Requires q 30-minute VS monitoring.
   d. Must include acute infusion reaction orders.

10. Each patient’s current TB and hepatitis B status should be known and documented prior to initiating the first dose.
    a. True.
    b. False.

ANSWERS
Volume 6: Monoclonal Antibodies

To obtain continuing education credit, please complete information in full.
Please print clearly:

Name: ____________________________________________

Address: __________________________________________

City: __________________________ State: _______ Zip: __________

License Number: ______________________ (required to receive CEs)

☐ RN       ☐ LPN       ☐ Certified Case Manager

Employer: __________________________________________

Work Phone: ________________________________________

Coram Representative: ___________________________ Date: __________

Was this material:

Useful in your practice?       ☐ Yes       ☐ No
Comprehensive enough?          ☐ Yes       ☐ No
Well organized?               ☐ Yes       ☐ No

☐ I would like my certificate emailed to me at: (ex: john.smith@coramhc.com)

☐ I would like my certificate mailed to the address provided above.