Immunosuppressants

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Immunosuppressive Agents

Very useful in minimizing the occurrence of exaggerated or inappropriate immune responses.

But these agents have the potential to cause disease and to increase the risk of infection and malignancies.

- The immune system protects the body against harmful foreign molecules
- This protection can result in serious problems. For example, an allograft can elicit a damaging immune response, causing rejection of the transplanted tissue

- Earlier drugs were nonselective and cause infection due to suppression of both the antibody-mediated (humoral) and cell-mediated arms of the immune system.
- Today, the principal approach to immunosuppressive therapy is to alter lymphocyte function using drugs or antibodies against immune proteins.
- Drugs are now available that more selectively and prevent the patient from becoming immunologically compromised

- Use in combination (because of severe toxicities when use as monotherapy)
- Immunosuppressive drug regimens usually consist of anywhere from two to four agents with different mechanisms of action that disrupt various levels of T-cell activation.
- Use to inhibit rejection of transplanted tissues
- Use in the treatment of autoimmune diseases.

Immunosuppressive Drugs:

1. Agents interfere with cytokine production or action.
2. Agents disrupt cell metabolism, preventing lymphocyte proliferation
3. Mono- and polyclonal antibodies block T-cell surface molecules.

Immunosuppressants

1-Selective Inhibitors of Cytokine

- Cytokines activate natural killer cells, macrophages and cytotoxic T lymphocytes.

Cyclosporine

- Selective Inhibitors of Cytokine that interfere with the production or activity of IL-2 & significantly depress the immune response and decrease graft rejection.

Pharmacokinetic of Cyclosporine

- Cyclosporine may be given intravenously or orally
- Slowly and incompletely absorbed (20-50%). metabolized by the P450 3A4
- Excretion of the metabolites is through the biliary route, a small fraction of the parent drug appearing in the urine
- Cyclosporine solution is now available for severe dry eye syndrome
- Inhaled cyclosporine for use in lung transplantation.

Indication of Cyclosporine

Cyclosporine may be used alone or in combination with other immunosuppressants, glucocorticoids or methotrexate

- It is immunosuppressant for transplantation of the kidney, pancreas, liver and cardiac transplantation
- Indicated in Autoimmune disorders, rheumatoid arthritis, psoriasis and asthma

Adverse Effects

1. Nephrotoxicity (aminoglycoside antibiotics and anti-inflammatories, potentiate it)
2. Hepatotoxicity
3. Viral infections (herpes group and cytomegalovirus)
4. Lymphoma &other cancers (Kaposi's sarcoma, skin cancer)
5. Anaphylactic reactions (on parenteral administration).
6. Hypertension, hyperlipidemia and hyperkalemia.
7. Tremor, seizures
8. Hirsutism
9. Hyperglycemia
10. Gum hyperplasia

Tacrolimus

- Have similar mechanism of action of Cyclosporine
- It is approved for the prevention of rejection of liver and kidney transplants and is given with a corticosteroids and/or an antimetabolite.
- Administered orally or intravenously
- Half-life of the intravenous form is approximately 9-12 hours.
- It is metabolized primarily by P450
- Ointment preparation for moderate to severe atopic dermatitis and psoriasis

Tacrolimus Has Found Favor Over Cyclosporine Because:

1. It is potent
2. Decreased episodes of rejection
3. Lower doses of corticosteroids can be used

Adverse Effects of Tacrolimus

1. Nephrotoxicity
2. Tremor, seizures and hallucinations are more severe than Cyclosporine
3. Hyperglycemia
4. Hypertension
5. Hyperlipidemia
6. Hyperkalemia
7. Gastrointestinal complaints
8. Anaphylactoid reactions

Note: Drug drug interaction are the same as those described for Cyclosporine

2-Immunosuppressive Antimetabolites

- They are generally used in combination with corticosteroids, CsA and TAC.

Azathioprine

- It is used in organ transplantation.
- It is converted first to 6-MP and then to the corresponding nucleotide.
- Lymphocytes are predominantly affected by the cytotoxic effects of azathioprine (Because of their rapid proliferation in the immune response and their dependence on the de novo synthesis of purines required for cell division)

Phrmacokinetic of Azathioprine

- It is well absorbed from the gastrointestinal tract
- It is metabolized primarily to mercaptopurine
- Xanthine oxidase converts the active material to 6-thiouric acid prior to excretion in the urine.
- Small amounts of unchanged drug are also excreted in the urine.
- Toxicity may occur in anephric or anuric patients.
- Allopurinol, inhibits the metabolism of azatihioprine (the dose of azathioprine reduced to prevent excessive toxicity)

Adverse Effect of Azathioprine and Mercaptopurine

- Bone marrow suppression, leukopenia, anemia & thrombocytopenia
- Skin rashes & fever
- Gastrointestinal symptoms seen mainly at higher dosages nausea and vomiting, diarrhea
- Hepatic dysfunction & mild jaundice

Mycophenolate Mofetil

- Oral and intravenous administration

Mechanism of Action of Mycophenolate

- It is rapidly hydrolyzed in the gastrointestinal tract to mycophenolic acid, it prevent the rapid proliferating T and B cells

Note: Lymphocytes lack the salvage pathway for purine synthesis and dependent on de novo purine production

Indication of Mycophenolate Mofetil

- Solid organ transplant patients for refractory rejection in combination with prednisone, as an alternative to cyclosporine or tacrolimus in patients who do not tolerate those drugs.
- First-line drug for preventing or reducing chronic allograft vasculopathy in cardiac transplant recipients
- Prophylaxis and treatment of both acute and chronic graft-versus-host disease in hematopoietic stem cell transplant patients (bone marrow transplant)
- lupus, nephritis, rheumatoid arthritis, inflammatory bowel disease, and some dermatologic disorders

Adverse Effects of Mycophenolate Mofetil

- Gastrointestinal disturbances (nausea and vomiting, diarrhea, abdominal pain)
- Headache
- Hypertension
- Reversible myelosuppression, neutropenia

3-Antibodies

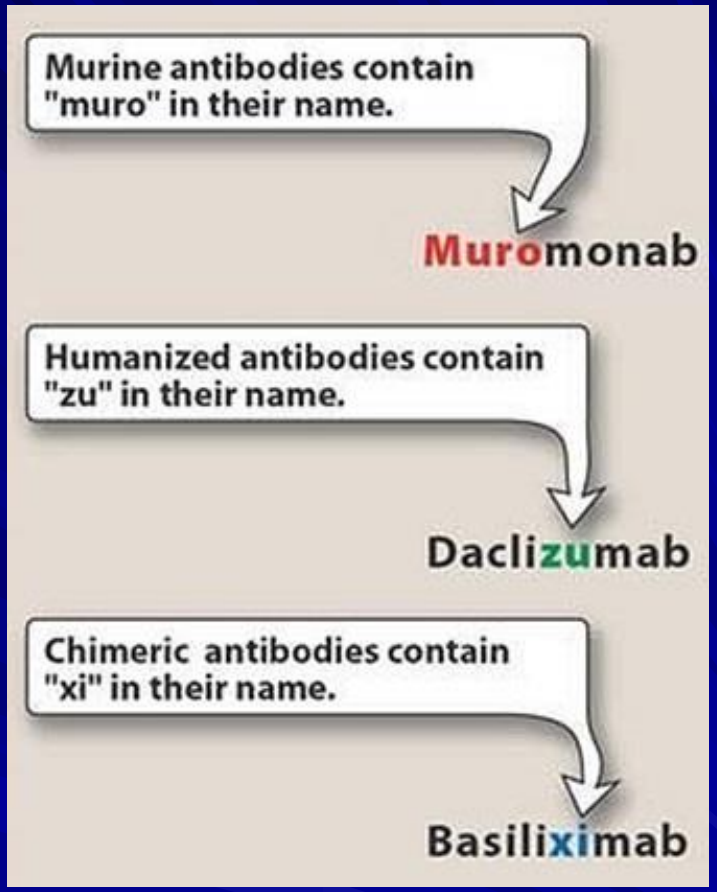
They prolonging allograft survival, they are prepared either by:

- Immunization of rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies directed against a number of lymphocyte antigens).
- Producing antigen-specific, monoclonal antibodies.

Note: Monoclonal antibodies directed against specific cell surface and soluble proteins such as CD3, CD4, CD25, CD40 and TNF-α. The high specificity of these antibodies improves selectivity and reduces toxicity of the therapy.

Conventions for Naming Monoclonal Antibodies.

Note: Muromonab was named before the convention was adopted to make the last three letters in their names mab



Muromonab-CD3

Mechanism of Action

- Binding to the CD3 protein results in a disruption of T-lymphocyte function
- Administered intravenously

Indication of Muromonab-CD3

- Treatment of acute rejection of renal allografts (Used with lower doses of steroids or other immunosuppressive drugs)
- Corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.
- It is also used to deplete T cells from donor bone marrow prior to transplantation.

Adverse Effects

- Anaphylactoid reactions
- Cytokine release syndrome (mild flu-like illness to a life-threatening, shock-like reaction).
- Fever
- Central nervous system effects

IL-2-receptor Antagonists
Basiliximab and Daclizumab

- Basiliximab is a chimeric mouse-human IgG1 that binds to CD25 of the IL-2 receptor alpha chain on activated lymphocytes.
- Daclizumab is a humanized IgG1 that also binds to the alpha subunit of the IL-2 receptor.

Mechanism of Action

- Basiliximab more potent than daclizumab
- Both antibodies are given intravenously
- Both compounds are anti-CD25 antibodies and bind to the chain of the IL-2 receptor on activated T cells. They thus interfere with the proliferation of these cells.

Indication of Basiliximab and Daclizumab

- Immunosuppressant.
- Both agents have been approved for prophylaxis of acute rejection in renal transplantation in combination with cyclosporine A and corticosteroids.

Alemtuzumab

- It is a humanized IgG 1 binds to CD52 found on normal and malignant B and T lymphocytes, NK cells, monocytes, macrophages and a small population of granulocytes
- Used for the treatment of refractory B-cell chronic lymphocytic leukemia.

Side Effects

- Cytokine release syndrome
- Hematologic toxicity, lymphopenia thrombocytopenia, neutropenia, anemia and pancytopenia.
- Opportunistic infections

4-Corticosteroids

The first pharmacologic agents used as immunosuppressives both

- In transplantation used in combination with other drugs for attenuating rejection episodes (prednisone or methylprednisolone)
- In various autoimmune disorders (prednisone or prednisolone)

Note: The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease and they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus and asthma.

Rh o (D) Immune Globulin Micro-Dose

This technique is based on the observation that a primary antibody response to a foreign antigen can be blocked if specific antibody to that antigen is administered passively at the time of exposure to antigen.

- Rh o (D) immune globulin is administered to the mother and must not be given to the infant.

- Rh o (D) immune globulin is a concentrated (15%) solution of human IgG containing a higher titer of antibodies against the Rh o (D) antigen of the red cell.
- If an injection of Rh o (D) antibody is administered to the mother within 24–72 hours after the birth of an Rh-positive infant, the mother's own antibody response to the foreign Rh o (D)-positive cells is suppressed because the infant's red cells are cleared from circulation before the mother can generate a B-cell response against Rh o (D).
- Prevent the development of erythroblastosis Fetalis with subsequent pregnancies (hemolytic disease of the newborn

- Treatment for Rh-negative mothers antepartum at 26-28 weeks' gestation who have had miscarriages, ectopic pregnancies, or abortions, when the blood type of the fetus is unknown.
- The usual dose of Rh o (D) immune globulin is 2 mL intramuscularly, containing approximately 300 mcg anti-Rh o (D) IgG.

Adverse Reactions

- Local discomfort at the injection site
- Slight temperature elevation.

Clinical Uses of Immunosuppressive Agents.

Source	Immunopharmacologic Agents Used	Response
Autoimmune diseases		
Idiopathic thrombocytopenic purpura (ITP)	Prednisone,[1] vincristine, occasionally cyclophosphamide, mercaptopurine, or azathioprine; commonly high-dose gamma globulin, plasma immunoadsorption or plasma exchange	Usually good
Autoimmune hemolytic anemia	Prednisone,[1] cyclophosphamide, chlorambucil, mercaptopurine, azathioprine, high-dose gamma globulin	Usually good
Acute glomerulonephritis	Prednisone,[1] mercaptopurine, cyclophosphamide	Usually good
Acquired factor XIII antibodies	Cyclophosphamide plus factor XIII	Usually good
Autoreactive tissue disorders (autoimmune diseases)[2]	Prednisone, cyclophosphamide, methotrexate, interferon-α and -β, azathioprine, cyclosporine, infliximab, etanercept, adalimumab	Often good, variable
Isoimmune disease		
Hemolytic disease of the newborn	Rh_o(D) immune globulin	Excellent
Organ transplantation		
Renal	Cyclosporine, azathioprine, prednisone, ALG, OKT3, tacrolimus, basiliximab,[3] daclizumab,[3] sirolimus	Very good
Heart	Cyclosporine, azathioprine, prednisone, ALG, OKT3, tacrolimus, basiliximab,[3] daclizumab,[3] sirolimus	Good
Liver	Cyclosporine, prednisone, azathioprine, tacrolimus, sirolimus	Fair
Bone marrow	Cyclosporine, cyclophosphamide, prednisone, methotrexate, ALG	Good
Prevention of cell proliferation		
Coronary stents	Sirolimus (impregnated stent)	Good
Neovascular macular degeneration	Ranibizumab (labeled), bevacizumab (off-label)	Fair