

Immunosuppressants

- The immune system plays an important role in protecting the body against harmful foreign molecules
- Immune system protection can result in serious problems
 - **Rejection** of transplanted tissue
 - **Autoimmune diseases**

- The introduction of an allograft can elicit a damaging immune response, causing rejection of the transplanted tissue
- Drugs can selectively inhibit rejection of transplanted tissues while preventing the patient from becoming immunologically compromised
- Immunosuppressive therapy alters lymphocyte function using drugs or antibodies against immune proteins

- Immunosuppressive therapy is used in the treatment of autoimmune diseases
 - Corticosteroids can control acute glomerulonephritis

- Immunosuppressive drug regimens usually consist of 2-4 agents with different mechanisms of action that disrupt various levels of T-cell activation
- Immunosuppressive drugs can be categorized according to their mechanisms of action
 - Agents that interfere with cytokine production or action
 - Agents that disrupt cell metabolism, preventing lymphocyte proliferation
 - Antibodies that block T-cell surface molecules

Selective inhibitors of cytokine production and function

- Cyclosporine (Deximune[®], Sandimmun[®])
- Tacrolimus (Prograf[®])
- Sirolimus (Rapamune[®])
- Everolimus (Certican[®])

Cyclosporine

- Uses

- To prevent **rejection** of kidney, liver, and cardiac allogeneic transplants
 - Combined with corticosteroids and an anti-metabolite such as mycophenolate mofetil
- Alternative to methotrexate for the treatment of severe active **rheumatoid arthritis**
- Recalcitrant **psoriasis** that does not respond to other therapies
- **Xerophthalmia**

MOA

- Suppresses cell mediated immune reactions
- Causes a decrease in IL-2
 - Primary chemical stimulus for increasing the number of T lymphocytes
- *Cyclosporine may be given either orally or by intravenous (IV) infusion.*

Adverse effects

- Nephrotoxicity
 - Monitor **blood levels** and monitor **kidney function**
 - Coadministration of drugs that can cause kidney dysfunction (aminoglycoside antibiotics, anti-inflammatories, such as diclofenac, naproxen, or sulindac) can **potentiate the nephrotoxicity**

Hepatotoxicity

Infections

Lymphoma

Anaphylactic reactions

Hypertension

Hyperlipidemia

Hyperkalemia

Tremor

Hirsutism

Glucose intolerance

Gum hyperplasia

Tacrolimus

- Approved for the prevention of rejection of liver and kidney transplants
- Given with a corticosteroid and/or an antimetabolite
- Gained favor over cyclosporine because of its
 - potency and decreased episodes of rejection and of
 - lower doses of corticosteroids used

- may be administered orally or IV
- Causes a decrease in IL-2
- Adverse effects
 - Nephrotoxicity
 - Neurotoxicity (tremor, seizures, and hallucinations)
 - Posttransplant insulin-dependent diabetes mellitus
 - Anaphylactoid reactions to the injection

Sirolimus

- Approved in renal transplantation
- Can be used together with cyclosporine and corticosteroids, allowing lower doses of those medications to be used
- The combination of **sirolimus** and **cyclosporine** is **synergistic** because sirolimus works later in the immune activation cascade
- drug is available as an oral solution or tablet.

- Adverse effects
 - Hyperlipidemia
 - Nephrotoxicity
 - Leukopenia
 - Thrombocytopenia
 - Impaired wound healing

Immunosuppressive Antimetabolites

- Azathioprine (Imuran[®], Azopi[®])
- Mycophenolate mofetil (Cellcept[®])

Azathioprine

- A prodrug that is converted first to **6-mercaptopurine** (6-MP) and then to the nucleotide, thioinosinic acid
- Rapid proliferation is important for the immune response which depends on the de novo synthesis of purines required for cell division, for lymphocytes in particular
- Adverse effects
 - Bone marrow suppression

Mycophenolate mofetil

- Used in heart kidney and liver transplants
- Rapidly hydrolyzed in the GI tract to mycophenolic acid a potent inhibitor of **inosine monophosphate dehydrogenase**, which blocks the formation of guanosine phosphate
 - depriving the rapidly proliferating T and B cells of a key component of nucleic acids

- Adverse effects
 - Diarrhea, nausea, vomiting, abdominal pain
 - Leukopenia
 - Anemia
- In an effort to minimize the GI effects associated with *mycophenolate mofetil*, enteric-coated mycophenolate sodium is contained within a delayed-release formulation

ANTIBODIES

- They are prepared by
 - immunization of either rabbits or horses with human lymphoid cells (producing a mixture of polyclonal antibodies or monoclonal antibodies) or
 - by hybridoma technology (producing antigen-specific monoclonal antibodies). Hybridomas are produced by fusing mouse antibody-producing

Antithymocyte globulins

- Antithymocyte globulins are polyclonal antibodies that are primarily used at the time of transplantation to **prevent early allograft rejection** along with other immunosuppressive agents.
- The antibodies bind to the surface of circulating T lymphocytes
- The antibody-bound cells are **phagocytosed** in the liver and spleen, resulting in lymphopenia and impaired T-cell responses.
- The antibodies are slowly infused intravenously, and their half-life
- extends from 3 to 9 days.

Muromonab-CD3 (OKT3)

- *Muromonab-CD3* is a murine (mouse) monoclonal antibody that is directed against the glycoprotein CD3 antigen of human T cells.
- indicated for the treatment of corticosteroid-resistant acute rejection of kidney, heart, and liver allografts.
- The drug has been discontinued from the market due to the availability of newer biologic drugs with similar efficacy and fewer side effects.

Basiliximab

- *Basiliximab* is said to be “chimerized” because it consists of 25% murine and 75% human protein.
- *Basiliximab* is approved for **prophylaxis of acute rejection in renal** transplantation in combination with *cyclosporine* and corticosteroids. It is not used for the treatment of ongoing rejection.

- Bind to IL-2 receptor on activated T cells, interfere with the proliferation of these cells
- *Basiliximab* is given as an IV infusion.
- The drug is generally well tolerated, with GI toxicity as the main adverse effect.

CORTICOSTEROIDS

- the first pharmacologic agents to be used as immunosuppressives, both in transplantation and in various autoimmune disorders.
- For **transplantation**, the most common agents are
 - *prednisone* and *methylprednisolone*, whereas
- **autoimmune** conditions (refractory rheumatoid arthritis, systemic lupus erythematosus, and asthma).
 - *prednisone* and *prednisolone*

- The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear.
- The T lymphocytes are affected most. The steroids are able to rapidly reduce **lymphocyte populations** by lysis or redistribution.
- On entering cells, they bind to the glucocorticoid receptor
- The complex passes into the nucleus and regulates the translation of DNA
- Among the genes affected are those involved in inflammatory responses

- The use of these agents is associated with numerous adverse effects.
 - they are **diabetogenic** and can with prolonged use
 - cause **hypercholesterolemia**,
 - **cataracts**,
 - **osteoporosis**, and
 - **hypertension**

		DRUG	ACTION	ADVERSE EFFECTS
<pre> graph TD A[Antigen] --> B[T-cell receptor] B --> C[Activated calcineurin] C --> D[Dephosphorylation of NFATc] D --> E[IL-2 gene promotion] E --> F[IL-2] F --> G[IL-2 receptors] G --> H[Progression into cell cycle] H --> I[Cell proliferation] B -.-> Inhibits B F -.-> Inhibits G H -.-> Inhibits H </pre>		Antithymocyte globulins	Destruction of T lymphocytes	Profound immunosuppression, fever, chills, and cytomegalovirus infection
		<i>Muromonab-CD3</i>	Destruction of T lymphocytes	Cytokine-release syndrome
		<i>Cyclosporine</i>	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, hepatotoxicity, hypertension, hyperlipidemia, hyperkalemia, gingival hyperplasia, and hirsutism
		<i>Tacrolimus (FK506)</i>	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, diabetes, alopecia, diarrhea
		<i>Basiliximab</i>	Blocks the IL-2 receptor	Gastrointestinal disorders
		<i>Siroliimus</i>	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea, delayed wound healing
		<i>Everolimus</i>	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, constipation, delayed wound healing, anemia, angioedema
		<i>Azathioprine</i>	Inhibits purine synthesis	Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia
		<i>Mycophenolate mofetil</i>	Inhibits purine synthesis	GI upset, nausea, diarrhea, leukopenia, tumors, increased susceptibility to infection