Immunosuppressants

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- 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

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- 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

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

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- 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

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Selective inhibitors of cytokine production and function

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

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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

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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.

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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

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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

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- 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

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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.

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

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Immunosuppressive Antimetabolites

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

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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

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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

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- 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

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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

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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.

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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.

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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.

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- 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.

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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*

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- 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

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- 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

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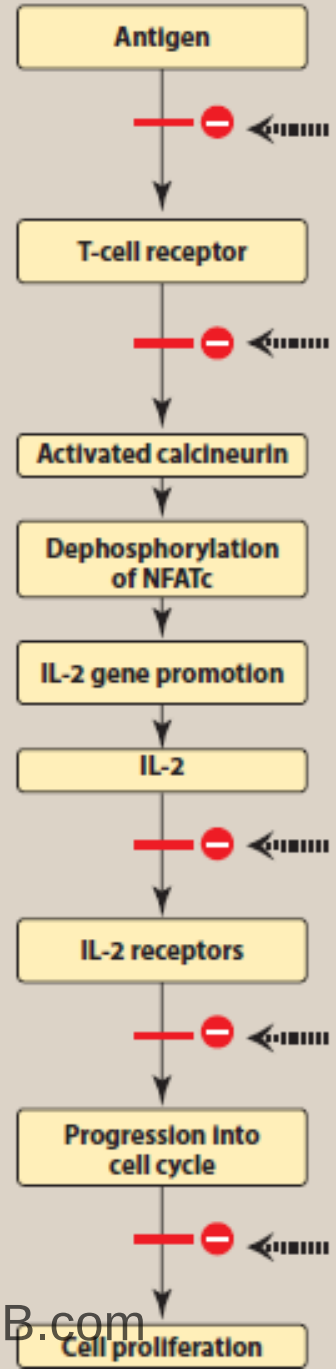

DRUG	ACTION	ADVERSE EFFECTS
Antithymocyte globulins	Destruction of T lymphocytes	Profound immunosuppression, fever, chills, and cytomegalovirus infection
Muromonab-CD3	Destruction of T lymphocytes	Cytokine-release syndrome
Cyclosporine	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, hepatotoxicity, hypertension, hyperlipidemia, hyperkalemia, gingival hyperplasia, and hirsutism
Tacrolimus (FK506)	Blocks calcineurin and inhibits IL-2 synthesis	Nephrotoxicity, neurotoxicity, diabetes, alopecia, diarrhea
Basiliximab	Blocks the IL-2 receptor	Gastrointestinal disorders
Sirolimus	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea, delayed wound healing
Everolimus	Blocks cytokine-stimulated cell proliferation	Hyperlipidemia, constipation, delayed wound healing, anemia, angioedema
Azathioprine	Inhibits purine synthesis	Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia, neoplasia
Mycophenolate mofetil	Inhibits purine synthesis	GI upset, nausea, diarrhea, leukopenia, tumors, increased susceptibility to infection

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