

Immunosuppressant drugs 2

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II: IMMUNOSUPPRESSIVE ANTIMETABOLITES

Immunosuppressive antimetabolite agents are generally used in combination with corticosteroids and calcineurin inhibitors, cyclosporine and tacrolimus.

A. Azathioprine (*Imuran*)

Azathioprine was the first for use in organ transplantation.

- The immunosuppressive effects of azathioprine are due to nucleotide analogue.
- The drug has little effect on suppressing a chronic immune response.
- Its major toxicity is bone marrow suppression.
- Concomitant use with angiotensin-converting enzyme inhibitors or cotrimoxazole can lead to an exaggerated leukopenic response.
- Allopurinol significantly inhibits the metabolism of azathioprine.

B. Mycophenolate mofetil

Mycophenolatemofetil has replaced azathioprine because of its safety and efficacy in prolonging graft survival.

It has been successfully used in heart, kidney, and liver transplants.

- Like 6-MP, it deprives rapidly proliferating T and B cells of a key component of nucleic acids
- The most common adverse effects include diarrhea abdominal pain
- leukopenia, and anemia.

III: ANTIBODIES

The use of antibodies plays a central role in prolonging allograft survival.

- The suffix “mab” (**monoclonal antibody**) identifies the category of drug.
- The **polyclonal antibodies**, although relatively inexpensive to produce, are variable and less specific, which is in contrast to monoclonal antibodies, which are homogeneous and specific.

A. Antithymocyte globulins

They are primarily used, together with other immunosuppressive agents, at time of transplantation to prevent early allograft rejection

- used to treat severe rejection episodes or corticosteroid-resistant acute rejection.
- The antibody-bound cells are phagocytosed in the liver and spleen, resulting in lymphopenia and impaired T-cell responses.
- adverse effects include chills and fever, leukopenia and thrombocytopenia, infections due to CMV or other viruses, and skin rashes.

B. Muromonab-CD3 (OKT3)

Muromonab-CD3 is a monoclonal antibody directed against glycoprotein CD3 antigen of human T cells.

Muromonab-CD3 is used for:

1. treatment of acute rejection of renal allografts
2. corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.
3. used to deplete T cells from donor bone marrow prior to transplantation.

Adverse effects:

Anaphylactoid reactions may occur.

- Cytokine release syndrome may follow the first dose. (The symptoms can range from a mild, flu-like illness to a life-threatening, shock-like reaction.)
- High fever
- CNS effects, such as seizures, encephalopathy, cerebral edema, headache.
- Infections can increase (some due to CMV).

Muromonab-CD3 is contraindicated

1. in patients with a history of seizures
2. in those with heart failure
3. in pregnant women,
4. breast-feeding.

C. IL-2-receptor antagonists

Basiliximabis , Daclizumab

- Both agents are used for prophylaxis of acute rejection in renal transplantation
- They are not used for the treatment of ongoing rejection

Mechanism of action:

Both compounds are anti-CD25 antibodies and bind to IL-2 receptor on activated T cells.

They thus interfere with the proliferation of these cells.

- Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system.

Adverse effects:

Both daclizumab and basiliximab are well tolerated.

Their major toxicity is GI.

- No clinically relevant antibodies to the drugs have been detected, and malignancy does not appear to be a problem.

Both antibodies are given IV.

Alemtuzumab

Alemtuzumab, exerts its effects by causing profound depletion of T cells from the peripheral circulation.

- Alemtuzumab is currently approved for the treatment of refractory B-cell chronic lymphocytic leukemia.
- Although it is not currently approved for use in organ transplantation, it is being used in combination with sirolimus and low-dose calcineurin inhibitors at many transplant centers.

Side effects :

first-dose cytokine-release syndrome, requiring premedication with acetaminophen, diphenhydramine, and corticosteroids

- neutropenia, anemia, and, rarely, pancytopenia.
- B-cell mediated rejection and development of autoimmune disorders in a small number of patients

CORTICOSTEROIDS

The corticosteroids were the first pharmacologic agents to be used as immunosuppressives both in transplantation and in various autoimmune disorders.

They are still one of the mainstays for attenuating rejection episodes.

- For transplantation, the most common agents are prednisone or methylprednisolone suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease.
- prednisolone is used for autoimmune conditions. including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal arthritis, and asthma.
- The steroids are able to rapidly reduce lymphocyte populations.
- They bind to the glucocorticoid receptor. The complex passes into the nucleus and regulates the translation of DNA.
- adverse effects: diabetogenic and can cause hypercholesterolemia, cataracts, osteoporosis, and hypertension with prolonged use.

Thank You