

IMMUNOMODULATORS

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TYPES OF IMMUNOMODULATORY DRUGS

Immunosuppressants

- Transplantation
- Autoimmune diseases
- Hemolytic disease of the newborns

Immunostimulants

- Immunodeficiency
- Chronic infectious diseases
- Tumors

Note: Immunization

- Active immunization: Vaccines
- Passive immunization: immunoglobulins

IMMUNOSUPPRESSANT DRUGS

Used to dampen the immune response

- Organ transplantation
- Autoimmune disease

Major classes:

- Glucocorticoids (prednisone, prednisolone)
- Calcineurin inhibitors (cyclosporine, Tacrolimus)
- Antiproliferative/Antimetabolic agents (Mycophenolate mofetil, azathioprine, Sirolimus)
- Biologicals (Antibodies)

Therapies require life-long use and expose patients to higher risk of infection and cancer

SITES OF ACTION OF IMMUNOSUPPRESSANTS INHIBITING T CELL ACTIVATION

<u>Drug</u>	<u>Targets</u>
<i>Glucocorticoids</i>	GRE of DNA (regulate gene transcription, inhibit transcription)
<i>Cyclosporine and Tacrolimus</i>	Calcineurin (inhibits the phosphatase activity required for IL-2 transcription)
<i>Sirolimus</i>	Protein kinase involved in cell-cycle progression (inhibits mTOR and IL-2 signaling)
<i>Azathioprine</i>	DNA synthesis
<i>Mycophenolate Mofetil</i>	Inosine monophosphate dehydrogenase (inhibits de novo guanine nucleotide synthesis)
<i>Muromonab-CD3</i>	T-cell receptor complex (blocks antigen presentation)
<i>Daclizumab, Basiliximab</i>	Anti-CD25 Abs; Block IL-2 receptor signaling

ANTIBODIES AS IMMUNOSUPPRESSANTS

Polyclonal antibodies against lymphocytes

- ⊠ Anti-thymocyte globulin (ATG)
- ⊠ Anti-lymphocyte globulin (ALG)
- ⊠ Raised in horses, rabbits, sheeps, or goats
- ⊠ Variable in efficacy and toxicity from batch to batch

Monoclonal antibodies

- ⊠ Anti-CD3
- ⊠ Anti-IL-2 receptor (CD25)
- ⊠ Anti-TNF- α
- ⊠ Anti-LFA-1

Antithymocyte Globulin-Rabbit (Thymoglobulin)

Rabbit gamma immune globulin preparation

Composed of antibodies to variety of T cell markers

Mechanisms

- Removal of T cells from circulation
- Modulation of T-cell activation, homing and cytotoxicity
- Decreases cytokine-induced reactions

Immunostimulants

Synthetic Stimulants (Levamisole; Ergamisol®)

- stimulates phagocytosis and T cell production of cytokines

Thalidomide (Thalomid®)

- Teratogenic
- Used in Erythema nodosum leprosum and multiple myeloma

Bacillus Calmette-Guérin (BCG)

- BCG is viable strain of *Mycobacterium bovis* that enhances macrophage activity
- Used for bladder cancer and melanomas

Immunostimulatory Cytokines

- ⊠ **Human recombinant IL-2 (Proleukin®)**
 - Enhance antitumor actions of cytotoxic T cells and NK cells
- ⊠ **Colony Stimulating Factors**
 - G-CSF (neutropenia) and GM-CSF (bone marrow transplant patients)
- ⊠ **Interferons**
 - IFN-alpha (anticancer uses)
 - IFN-beta (relapsing type multiple sclerosis)
 - IFN-gamma (chronic granulomatous disease)

Immune globulin

Passive immunization for congenital or acquired immunodeficiency

- High risk but no time for active immunization (vaccines)
- A disease is already present

Derived from pooled plasma

- Contains usually IgG (>95%)
- Non-specific vs. specific (hyperimmune)
- Cytomegalovirus immune globulin: Cytogam
- RSV (respiratory syncytial virus) : Respigam
- Rho(D) immune globulin: Rhogam, Bay-Rho-D, Winrho SDF, Micrhogam
- Intravenous immunoglobulin (IVIG): non-specific

Erythroblastosis fetalis (hemolytic disease of the newborn)

