



IMMUNOMODULATORS

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IMMUNE SYSTEM

- The immune system is designed to protect the host from invading pathogens and to eliminate disease.
 - a) Innate immune response
 - b) Adaptive immune response

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- **Innate immune response** – first line of defense against an antigenic insult. Includes defenses like physical (skin), biochemical (complement, lysozyme, interferons) and cellular components (neutrophils, monocytes, macrophages).
- **Adaptive immune response**
 - a) **Humoral immunity** - Antibody production – killing extracellular organisms.
 - b) **Cell mediated immunity** – cytotoxic / killer T cells – killing virus and tumour cells.

ABNORMAL IMMUNE RESPONSE

- Hypersensitivity reactions
 - Type 1 – Anaphylactic shock
 - Type 2 – mismatched blood transfusion
 - Type 3 – Serum Sickness, glomerulonephritis and arthritis.
 - Type 4 – TB, leishmaniasis.

- **Autoimmunity** – Autoimmune diseases arise when the body mounts an immune response against itself as a result of failure to distinguish self tissues and cells from foreign antigens.

Rheumatoid Arthritis, S.L.E, Type 1 Diabetes Mellitus, Multiple Sclerosis etc....

- **Immunodeficiency Diseases**

a) Congenital – Di George's syndrome, SCID due to ADA deficiency.

b) Extrinsic – HIV causing AIDS.

DEFINITION

Immunomodulators are drugs which either suppress the immune system –

Immunosuppressants

or

stimulate the immune system –

Immunostimulants.

IMMUNOSUPPRESSANTS

Glucocorticoids - Prednisolone.

Calcineurin inhibitors – Cyclosporine,
Tacrolimus.

Cytotoxic agents – Azathioprine, Leflunomide,
Cyclophosphamide, Methotrexate,
Dactinomycin, Vincristine.

Antibodies – ALG, ATG like Muromonab CD3,
IGIV, Monoclonal antibodies like Daclizumab,
Basiliximab.

Others – Interferons, Thalidomide, Sirolimus,
Mycophenolate Mofetil.

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USES OF IMMUNOSUPPRESSANTS

1) SOLID ORGAN AND BONE MARROW TRANSPLANTATION

Hyperacute rejection

Accelerated rejection

Acute rejection

Chronic rejection

2) AUTOIMMUNE DISORDERS

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CALCINEURIN INHIBITORS

- Cyclosporine –
 - fat soluble peptide antibiotic.
 - Binds to cyclophilin and inhibits a cytoplasmic phosphatase calcineurin which is necessary for activation of a T cell specific transcription (NFAT) which causes synthesis of IL-2 by activated T cells.
 - Metabolized by Cyt P450 – drug interactions
 - S.E – nephrotoxicity, hypertension, hyperglycaemia, liver dysfunction and hirsutism.
 - Very low incidence of bone marrow toxicity.
 - Used in renal, pancreatic and liver transplantation. Also in RA, psoriasis, uveitis and asthma.

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- Tacrolimus (FK 506)
 - Antibiotic.
 - Binds to FKBP-12.
 - It is 10-100 times more potent than cyclosporine in inhibiting the immune response.
 - Topical preparation available for use in atopic dermatitis and psoriasis.

- **Glucocorticoids** – Lympholytic activity, anti-inflammatory property.
- Used as 1st line immunosuppressive therapy in solid and hematopoietic stem cell transplant, ITP, RA etc....
- **Interferons** - IFN alpha- immune enhancing action - melanoma, RCC.
 - **IFN beta - multiple sclerosis**
 - **IFN gamma - chronic granulomatous disease.**
- **Sirolimus** – inhibits protein kinase and inhibits T cell response to IL-2.
 - **Blocks cell cycle progression**

- **Thalidomide** – inhibits angiogenesis, reduces phagocytosis, enhances cell mediated immunity
 - **Increases levels of IL-10.**
 - **Used in multiple myeloma, graft versus host disease, myelodysplastic syndrome, RCC, prostrate Ca, colon Ca.**
- **Mycophenolate Mofetil** – mycophenolic acid
 - **Inhibits inosine monophosphate dehydrogenase which is a key enzyme in guanine nucleotide synthesis.**
 - **Used in steroid refractory graft versus host disease, RA, SLE.**

Azathioprine

- Mercaptopurine –
 - interferes with purine nucleic acid metabolism and incorporates false nucleotide.
 - Used in Renal allograft, RA, SLE, ITP, Crohn's disease, glomerulonephritis.

- **Leflunomide** – it inhibits pyrimidine synthesis. Used in RA.
- **Cyclophosphamide** – alkylating agent which destroys proliferating lymphoid cells. Used in SLE, autoimmune haemolytic anaemia, multiple sclerosis, Wegener's granulomatosis.
- **Muromonab CD3** – T cell receptor complex (blocks Ag recognition).
 - **Used in steroid resistant rejection.**
- **Daclizumab, Basiliximab** – IL-2 receptor (blocks IL-2 mediated T cell activation).
 - **Used in acute organ rejection in renal transplant patients.**

IMMUNOSTIMULANTS

- Used in immunodeficiency disorders, chronic infections and cancer.
- 1) **Cytokines** like INF alpha, INF beta, INF gamma
 - IL-2 – metastatic RCC and malignant melanoma.
 - TNF alpha- malignant melanoma and soft tissue sarcoma of extremity.
 - 2) **Levamisole** – anti helminthic.
 - Used to treat immunodeficiency associated with Hodgkins disease.
 - Causes severe agranulocytosis.

3) **BCG** – used as intravesical therapy for superficial bladder cancer.

It causes activation of macrophages to make them more effective killer cells.

4) **Other drugs** –

inosiplex, azimexon, imexon, thymosin, methylinosine monophosphate.....