IMMUNOSUPRESSANT DRUGS

SOURCES:
BERTRAM G. KATZUNG BASIC & CLINICAL PHARMACOLOGY 15TH EDITION
GOODMAN AND GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS 13TH EDITION.

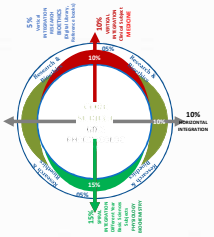
LEARNING OBJECTIVES

- At the end of the session, the students of 3rd year MBBS will be able to
- Recall the type of immune responses
- Classify immunosuppressant
- Discuss silent pharmacological features of each drug
- Identify the therapeutic uses and adverse effects of each drug

MOTTO AND VISION

- To impart evidence based research oriented medical education
- To provide best possible patient care
- To inculcate the values of mutual respect and ethical practice of medicine

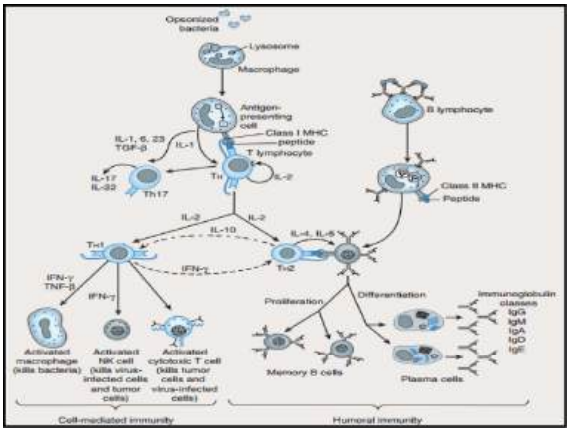
Prof. Umar's Clinically Oriented Integration Model For Basic Sciences Interactive Lectures



3rd Year Pharmacology LGIS	
Core Subject – 60%	
Pharmacology	
Horizontal Integration – 10%	
Same Year Subjects	• Pathology (10%)
Vertical Integration – 10%	
Clinical Subjects	• Medicine (10%)
Spiral Integration – 15%	
Different Year Basic Sciences Subjects	• Physiology (10%) • Biochemistry (5%)
Vertical Integration – 05%	
Research & Bioethics	

SPIRAL INTEGERATION/PHYSIOLOGY

IMMUNE SYSTEM



CORE SUBJECT

CLASSIFICATION

- **Calcineurin inhibitors (Specific T-cell inhibitors)**
  - Cyclosporine
  - Tacrolimus
- **Antiproliferative drugs (Cytotoxic drugs)**
  - Azathioprine
  - Cyclophosphamide
  - Methotrexate
  - Chlorambucil
  - Leflunomide
  - Hydroxychloroquine
  - Mycophenolate mofetil (MMF)

Continued…

- **Mammalian target of rapamycin (mTOR) inhibitors**
  - Sirolimus
  - Everolimus
  - Temsirolimus
- **Immunomodulatory derivatives of Thalidomide (IMiDs)**
  - Lenalidomide
  - Pomalidomide

Continued…

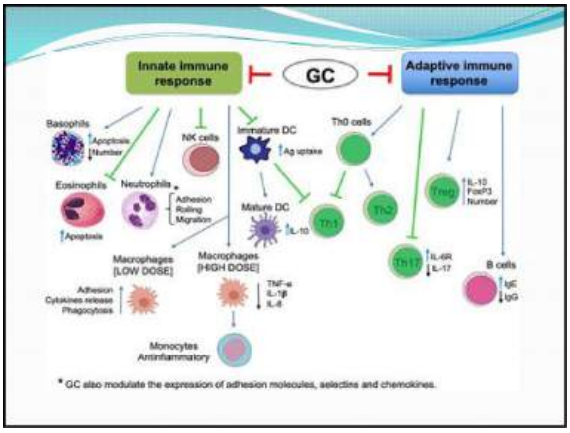
- **Glucocorticoids**
  - Prednisolone
- **Antibodies**
  - Antilymphocyte Globulin (ALG)
  - Antithymocyte Globulin (ATG)
  - Muromonab CD3
  - Rho (D) immune Globulin
  - Immune Globulin intravenous (IGIV)
  - Monoclonal Antibodies (MABs)

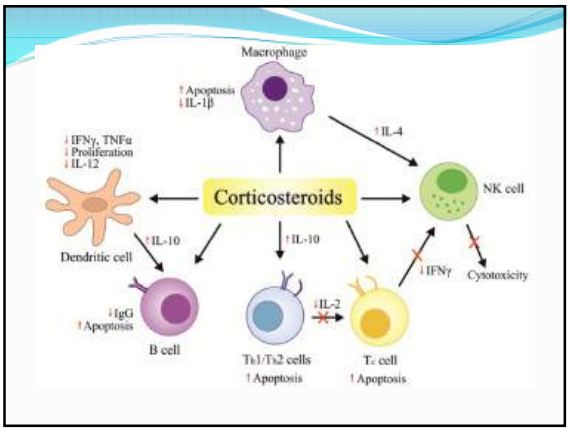
Inhibitors of cytokine gene expression

Corticosteroids

- Prednisone
- Prednisolone
- Methylprednisolone
- Dexamethasone

They have both anti-inflammatory action and immunosuppressant effects.





VERTICAL INTEGERATION/ MEDICINE

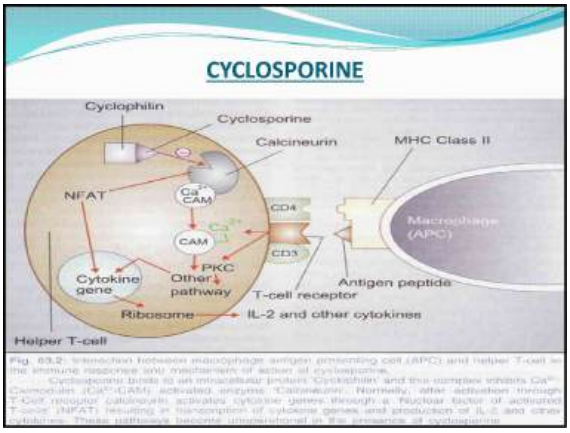
Indications

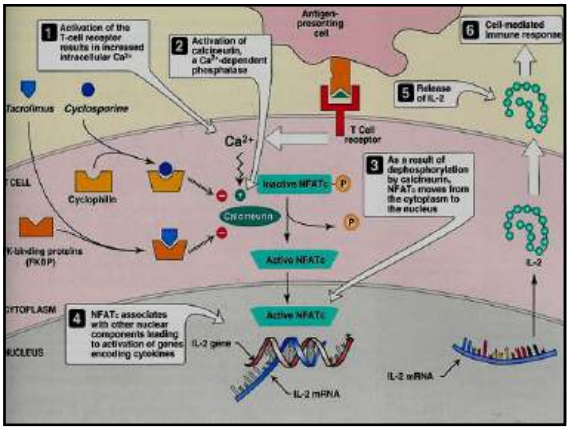
- Are first line therapy for solid organ allografts & haematopoietic stem cell transplantation.
- Autoimmune diseases as refractory rheumatoid arthritis, systemic lupus erythematosus, asthma
- Acute or chronic rejection of solid organ allografts.

Adverse Effects

- Adrenal suppression
- Osteoporosis
- Hypercholesterolemia
- Hyperglycemia
- Hypertension
- Cataract
- Infection

CORE SUBJECT





VERTICAL INTEGERATION/ MEDICINE

USES

- Dry eye syndrome
- Lung transplantation
- Organ Transplantation
- Graft–versus-host disease
- Autoimmune diseases

ADVERSE EFFECTS

- Nephrotoxicity
- Hypertension
- Hyperglycemia
- Liver dysfunction
- Hyperkalemia
- Altered mental status
- Increased incidence of lymphoma
- Viral infections
- Gum hyperplasia
- Little bone marrow toxicity
- hyperlipidemia

DRUG INTERACTIONS

- Nephrotoxic drugs
- Enzyme inhibitors
- Enzyme inducers
- K sparing diuretics

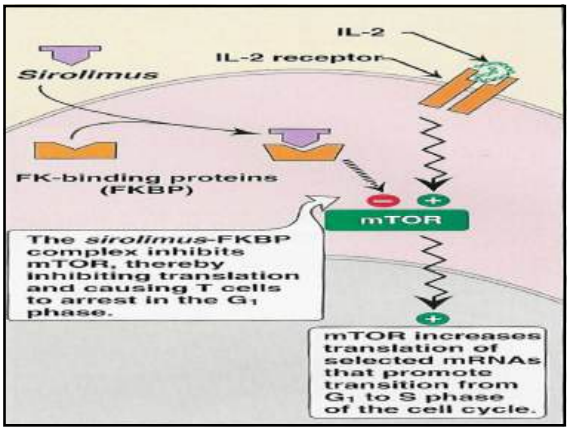
CORE SUBJECT

TACROLIMUS

- Not chemically similar to cyclosporine
- Binds to FK-binding proteins
- 10-100 times more potent
- Pharmacokinetics, uses, adverse effects
- Atopic dermatitis and psoriasis

SIROLIMUS(PROLIFERATION SIGNAL INHIBITOR,PSIs)

- Given orally
- liver metabolism
- Excretion through feaces



VERTICAL INTEGERATION/ MEDICINE

USES

- Prevent rejection of solid organ allografts
- Graft versus host disease
- Topically with cyclosporine in uveoretinitis.
- Sirolimus eluting coronary stents

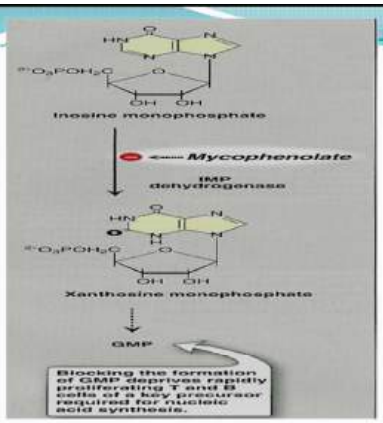
ADVERSE EFFECTS

- Myelosuppression
- Hepatotoxicity, Hyperlipidaemia
- Diarrhea, pneumonitis
- Hemolytic uremic syndrome

CORE SUBJECT

MYCOPHENOLATE MOFETIL

- Oral , im and iv
- Used in solid organ transplant, prevent chronic allograft vasculopathy in cardiac transplant, in hematopoietic stem cell transplant
- Autoimmune diseases



TOXICITY

- GIT disturbances
- Headache
- Hypertension
- Myelosuppression
- CI in pregnancy

LENALIDOMIDE

- Inhibits TNF- α
- Reduces phagocytosis by neutrophils
- Increases production of IL-10
- Alters adhesion molecule expression
- Enhances cell-mediated immunity via interactions with T cells

USES

- Multiple myeloma at initial diagnosis
- Myelodysplastic syndrome
- Acute myelogenous leukemia
- Graft-versus-host disease
- Erythema nodosum leprosum

ADVERSE EFFECTS

- Teratogenesis
- Peripheral neuropathy
- Constipation
- Hypothyroidism
- Increased risk of deep vein thrombosis

ANTILYMPHOCYTE & ANTITHYMOCYTE ANTIBODIES

- Acts primarily on the small, long-lived peripheral lymphocytes
- Thymus-dependent" lymphocytes from lymphoid follicles are also depleted
- Destruction of T cells, an impairment of delayed hypersensitivity and cellular immunity

Kinetics

- Given i.m. or slowly infused intravenously.
- Half life extends from 3-9 days.

Uses

- Combined with cyclosporine for bone marrow transplantation.
- To treat acute allograft rejection.
- Steroid-resistant rejection.

ADVERSE EFFECTS

- Local pain and erythema
- Skin-reactive and precipitating antibodies may be formed
- Anaphylactic and serum sickness reactions
- Increased risk of viral infections and cancer

IMMUNE GLOBULIN INTRAVENOUS (IGIV)

- Reduction of helper T cells
- Decrease spontaneous immunoglobulin production
- Increase antibody catabolism
- Use in different autoimmune diseases

Rho (D) IMMUNE GLOBULIN

- Concentrated (15%) solution of human IgG
- Used for prevention of Rh hemolytic disease of the newborn

HYPERIMMUNE IMMUNOGLOBULINS

- For tetanus, rabies, digoxin overdose, RSV,CMV, hep B

Monoclonal antibodies

DRUG	TARGET	USES
Adalimumab, certolizumab pegol, etanercept, golimumab, infliximab	TNF α	juvenile rheumatoid arthritis and similar inflammatory diseases such as psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis.
Abatacept and belatacept	CTLA-4	rheumatoid arthritis and organ transplant
Anakinra	IL-1	rheumatoid arthritis
Rilonacept	IL-1	rheumatoid arthritis
Ixekizumab, secukinumab,brodalumab	IL-17	plaque psoriasis

CONTINUED…

DRUG	TARGET	USES
Reslizumab,Mepolizumab	IL-5	eosinophilic asthma
Siltuximab	IL-6	multicentric Castleman's disease
Tocilizumab	IL-6	
Basiliximabis, Daclizumab	CD25, the IL-2 receptor α chain on activated lymphocytes.	prophylaxis of acute organ rejection in renal transplant patients
Belimumabis	inhibits B cell activating factor	

CONTINUED…

DRUG	TARGET	USES
Canakinumab	prevents IL-1βfrom binding to its receptor.	cryopyrin-associated periodic syndromes (CAPS
Natalizumab	binds to the α4-subunit of α4β1 and α4β7 integrins expressed on the surfaces of all leukocytes except neutrophils	multiple sclerosis and Crohn's disease
Omalizumab	anti-IgE recombinant	Asthma
Ustekinumab	blocks IL-12 and IL-23 from binding to their receptors,	plaque psoriasi

Immunosuppressant Drugs

Class	Examples	Mechanism
Calcineurin Inhibitors	Ciclosporin Tacrolimus	Calcineurin activates transcription of IL-2. Ciclosporin binds with cytosolic cyclophilin to form a complex which inhibits calcineurin.
mTOR Inhibitors	Sirolimus Temsirolimus Everolimus	Sirolimus binds to cytosolic FK-binding protein 12 (FKBP12). This complex inhibits mTOR, thereby blocking activation of B and T cells.
Antiproliferative Agents	Azathioprine Mycophenolic Acid	Azathioprine is an antimetabolite which interferes in purine biosynthesis which, in turn, disrupts DNA synthesis in the S-phase of the cell cycle. Mycophenolic acid inhibits the enzyme inosine monophosphate dehydrogenase, the enzyme needed for *de novo* synthesis of purines for B and T cells.
Interleukin-2 Receptor Antibodies	Basiliximab Daclizumab	Basiliximab binds to the α-subunit of the IL-2 receptor on activated T-cells, preventing their proliferation. Daclizumab binds to CD25, the alpha subunit of the IL-2 receptor on T-cells.

@PharmaFactz

mTOR = Target of Rapamycin (*former name of Sirolimus*)

RESEARCH

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Artificial Intelligence

- Yang Y, Zhao Y, Liu X, Huang J. Artificial intelligence for prediction of response to cancer immunotherapy. InSeminars in Cancer Biology 2022 Nov 11. Academic Press.
- Segú-Vergés C, Artigas L, Coma M, Peck RW. Artificial intelligence assessment of the potential of tocilizumab along with corticosteroids therapy for the management of COVID-19 evoked acute respiratory distress syndrome. PloS one. 2023 Feb 15;18(2):e0280677.

EOLA

1. Which of the following drug specifically inhibit calcenrin in the activated T lymphocytes?

a. Daclizumab
b. Tacrolimus
c. Prednisone
d. Sirolimus
e. Mycophenolate mofetil

- 2. which of the following drugs used to prevent allograft rejection can cause hyperlipidemia?

a. Azathioprine
b. Basiliximab
c. Tacrolimus
d. Mycophnolate mofetil
e. Sirolimus