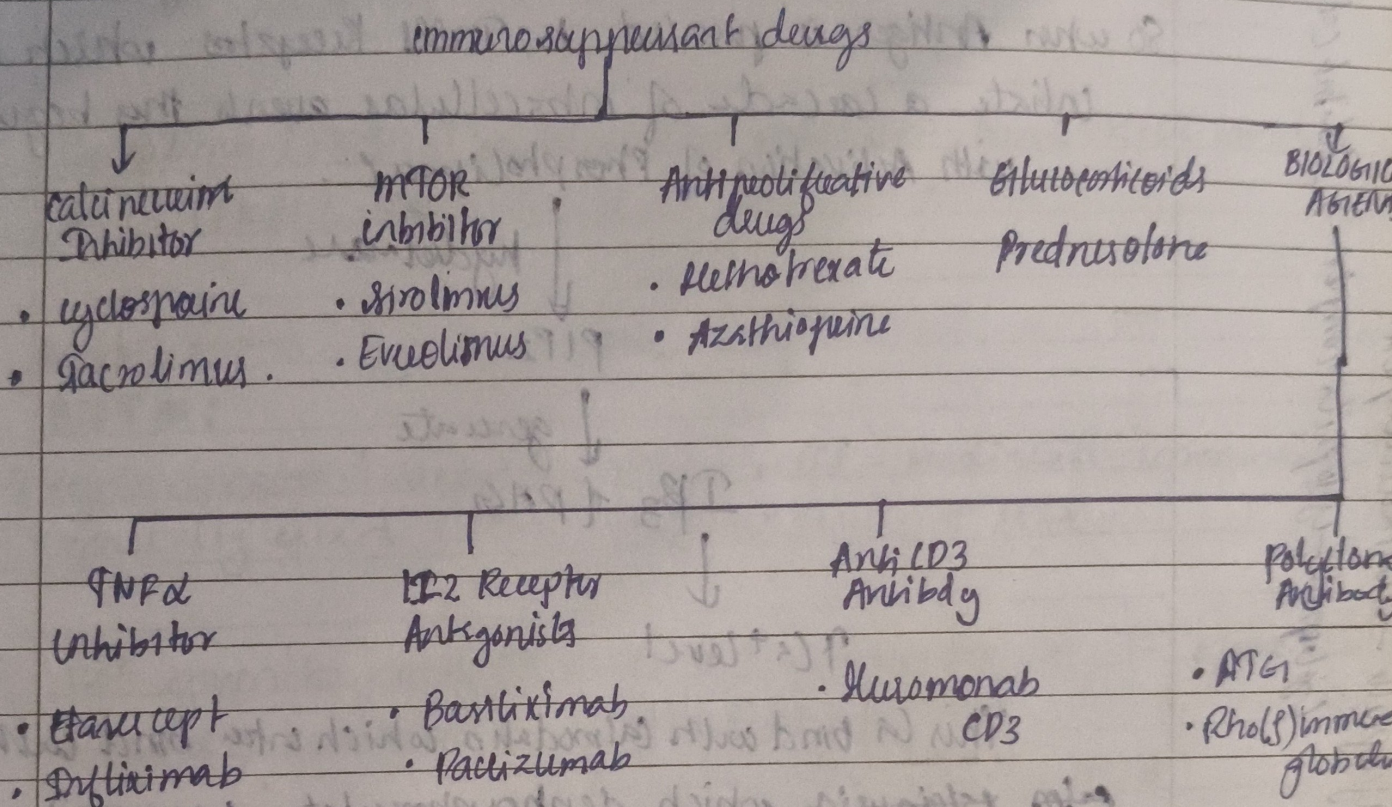


IMMUNOSUPPRESSANT DRUGS:

Immunosuppressant are drugs which inhibit cellular / humoral or both type of immune Response, major use is transplantation.



CALCINEURIN INHIBITORS: — cyclic polypeptide with 11 AA.

→ cyclosporine — used in organ transplant
→ Tacrolimus

→ cyclosporine mainly inhibit the synthesis of IL-2.

→ usually a macrophage ^{with} present a Antigen present it on MHC-II complex towards T cell

→ T cell to get Activated Require IL-2. (This process is inhibited)

↓ This Activation lead to

→ Cytotoxic T cell Activation

→ T-Helpere Activation

→ Plasma cell Activation (Antibody production)

CSF
CSF

→ Calcineurin Inhibitor Inhibit calcineurin

A key Protein to Allow transcription of IL-2 → T cell Activation

Process / Mechanism

So when Antigen is presented to T cell Receptor which will initiate a cascade of intracellular events this begins with Activation of Phospholipase.

↓ hydrolyze
PIP₂

↓ generate
IP₃ & DAG

↓
Ca²⁺ level

This Ca bind with calmodulin which then bind with calcineurin which dephosphorylate NFAT

(Nuclear factor of Activated T cell)

↓
which is needed for transcription of IL-2

↓
T cell Activation

High calcineurin is Inhibited by cyclophilin (CP)

↓
stop dephosphorylation

↓
T cell Inactivation

whereas → Tacrolimus binds to FKBP12 → bind to calmodulin the same process as (CP)

Cyclophilin - cyclophilin receptor → T cell activation

Summary:

- Cyclosporine: Calcineurin Inhibitor, binds cyclophilin. Block T-cell Activation by preventing T-cell transcription.

Uses: Hx of Psoriasis, RA

side/effect - hypertension, hyperlipidemia, gingival hyperplasia

Tacrolimus (FK506) - Calcineurin inhibitor, binds FK506-binding protein (FKBP). Blocks T-cell.

used: same

NOTE:

- cyclosporine suppresses only cell-mediated immunity.
- generally used with corticosteroids & Htx.
- not given to patients with K^+ supplements, K^+ sparing diuretics, ketoconazole, erythromycin.
- Tacrolimus ~100 mg twice daily
↓
Oral Absorption ↓ by food.
- careful if cyclosporin is not working.
- used in Crohn's disease.
- Atopic dermatitis, Hypertension

Ref: pig 64.2 p-982

Dacizone
Basiliximab

SIROLIMUS:

FKBP

- easier named as Rapamycin
- binds to sirolimus-FKBP complex that inhibit another kinase called sirolimus-FKBP complex



mammalian target of Rapamycin (mTOR)

↓
does not interact with calcineurin

- It acts the immune response at a later stage than cyclosporin so provided as Antiproliferative drug.
- used in steroid Refractory cases of stem cell transplant.

NOTE: sirolimus coated stents are being used to Reduce incidence of CAD.

S/E → cause thrombocytopenia, liver damage, diabetes

NOTE:

- Everolimus → better bioavailability, better orally absorbed.

ANTIPROLIFERATIVE DRUGS:

used in cancer chemotherapy which immunosuppress by preventing T & B lymphocytes.

AZATHIOPRINE: It is a purine Antimetabolite which has more immunosuppressant.

- Affect the differentiation of function of T cell inhibit cytolytic lymphocyte LMP is depressed.
- less effective than cyclophosphamide.

→ Recently Azathioprine has been found effective for Restenosis
new normal pig or vellozo

Methotrexate: folate Antagonist. depresses C.I.T
Anti-inflammatory Response.
used in RA, psoriasis, MG.

Cyclophosphamide: Marked effect on B cells & HSP. Not C.I.T

Hypophosphite mofetil (MMF): They inhibit inosine
monophosphate dehydrogenase → essential for de-
novo synthesis of guanosine nucleotide in T & B cells.

NOTE:

Glucocorticoids are most imp effective drug for the graft vs
host rxn.

→ cyclosporin + prednisolone + MMF - use mainly used. Tacrolimus
cause doesn't cause renal toxicity.