cyclosporine

MOA

cyclosporine

⇩

binds cyclophilin

⇩

complex inhibits calcineuria

⇩

inhibit T-cell

inhibit IL-2

USES

- prevent and treat graft-rejection.
- second line drug for treat Autoimmune diseases.
- Rheumatoid.
- psoriasis.

cyclosporine
- → oral + IV.
- → cyp3A4.
- → P-gp.
- → Excretion → biliary into feces.

S/E

- Nephrotoxicity → most common.
  - → monitor kidney.
  - → reduction dosage.
- Hepatotoxicity.
- Neurotoxicity.
- viral infection → herpes
  - → CMV
- Hypertension.
- Hyperlipidemia.
- Hyperglycemia.
- Hyperkalemia.
- Hirsutism.
- Gingival hyperplasia.

Drug-Drug interaction

- Aminoglycoside + NSAIDS = cause nephrotoxicity by themselve
- cyp3A4 inhibitor + P-gp inhibitor = impair cyclosporine metabolism

Tacrolimus

MoA Tacrolimus

⇩

bind FKBP

⇩

complex inhibits calcineurin

⇩

inhibit T-cell

inhibit IL-2

USES

- prevent and treat graft-rejection.
- Atopic dermatitis and psoriasis.

Tacrolimus

- → preferred over cyclosporine
- → oral + IV
- → cyp3A4/5
- → P-gp
- → Excretion → biliary in feces.
- → Absorption is decreased with → high-fat
  - → high carbohydrate meals

S/E

- nephrotoxicity + neurotoxicity
- post transplant insulin-dependent
- alopecia
- have similar toxicities of cyclosporine except → hirsutism
  - → gingival hyperplasia
- have lower incidence of cardiovascular toxicities than cyclosporine.

Drug-Drug interaction

- similar to cyclosporine

MOA

Belatacept

⇩

Bind CD80, CD86 (signal 2)

⇩

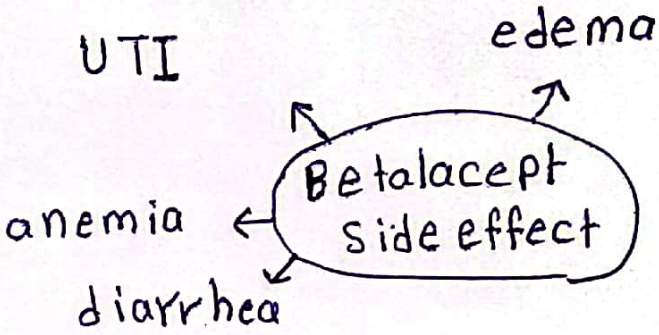
block CD28 of T-cell

⇩

inhibit T-cell
inhibit IL-2

Belatacept

S/E



uses

for Long-term maintenance

Belatacept
- → second-generation costimulation
- → targets signal 2
- → IV
- → dosed in two phases
  - → initial high-dose phase: (more frequent interval)
  - → maintenance phase: (once a month)
- → clearance is not affected.

MoA Sirolimus

⇩

Bind FKBP

⇩

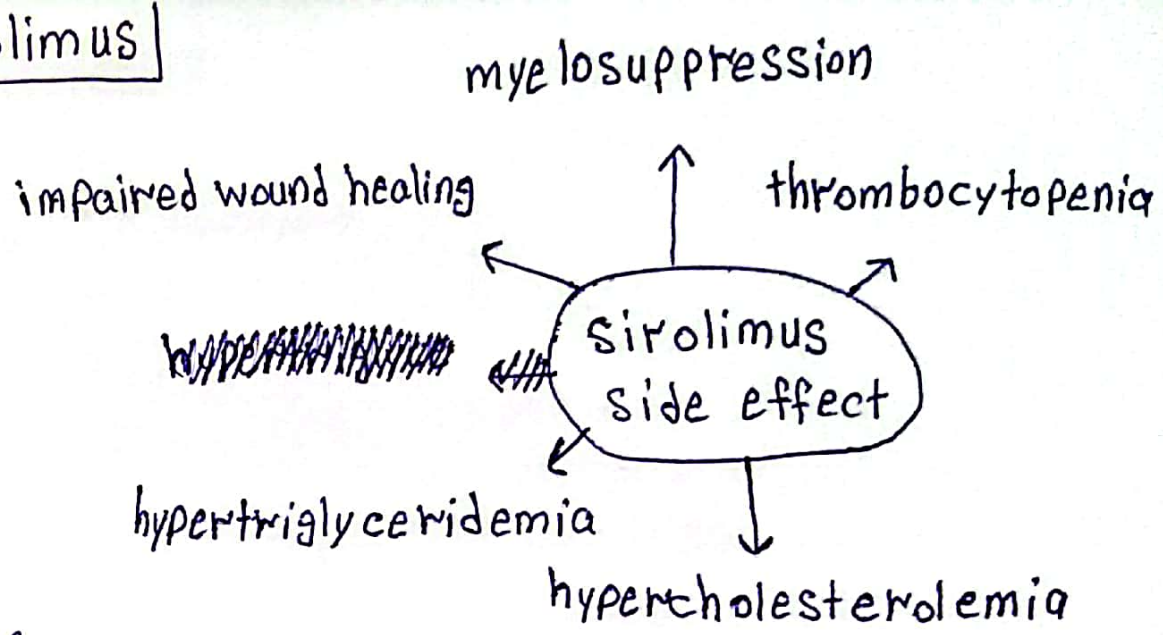
*inhibit mTOR

⇩

inhibit T-cell (Signal 3)

*unlike cyclosporine and tacrolimus, sirolimus does not lower IL-2 production, but, inhibit the cellular response to IL-2.

Sirolimus

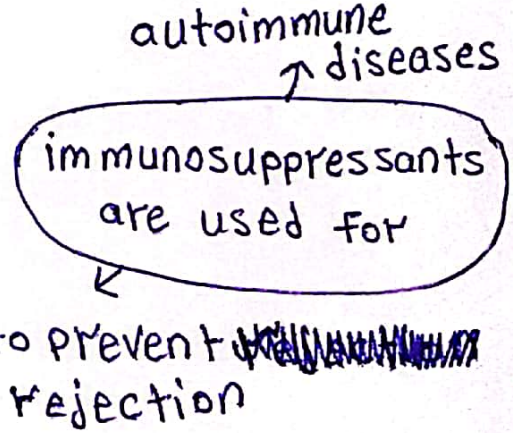


USES

- prevent rejection.
- coronary artery disease (stents reduce restenosis).

Sirolimus

- → oral
- → once-daily
- → Absorption decrease → high fat meals.
- → [redacted] CYP3A4
- → P-gp



* Everolimus → use in renal transplantation
  - → Absorption decreased → high-fat meals
  - → CYP3A4, P-gp
  - → not given with ACEIs.
  - → S/E → angioedema
    - → myelosuppression
    - → thrombocytopenia
    - → impaired wound healing
    - → hypertriglyceridemia
    - → hypercholesterolemia
    - → increased risk of kidney arterial and venous thrombosis.

mTOR inhibitor → everolimus
- ↑ sirolimus
- ↓ temsirolimus

Calcineurin inhibitors → tacrolimus
- ↑ cyclosporine

co-stimulation blockers → belatacept

* IL-2 → stimulate proliferation → T-cell (helper)

cytokines includes
- ↑ INFs
- ← ILs
- → TNFs
- ↓ Transforming growth factors
- ↓ colony stimulating factor

* immunosuppressive antimetabolite + calcineurin inhibitors + corticosteroids = (√)

immunosuppressive antimetabolite → Azathioprine

↓

mycophenolate mofetil

* Azathioprine: → prodrug

→ converted → (6-MP)

→ thioinosinic acid

→ cytotoxic effect

rapid proliferation in the immune response

dependence on the de nove synthesis purines

→ S/E → myelosuppressi

* Mycophenolate mofetil:

→ replaced Azathioprine —due to→ prolonging graft survival

→ used transplants → heart.
→ kidney.
→ liver.

→ inhibitor of inosine monophosphate dehydrogenase.

→ block de nove formation guanosine phosphate.

→ S/E → diarrhea + nausea + vomiting + abdominal pain.

→ high doses → CMV infection.

→ Drug-Drug interaction:-

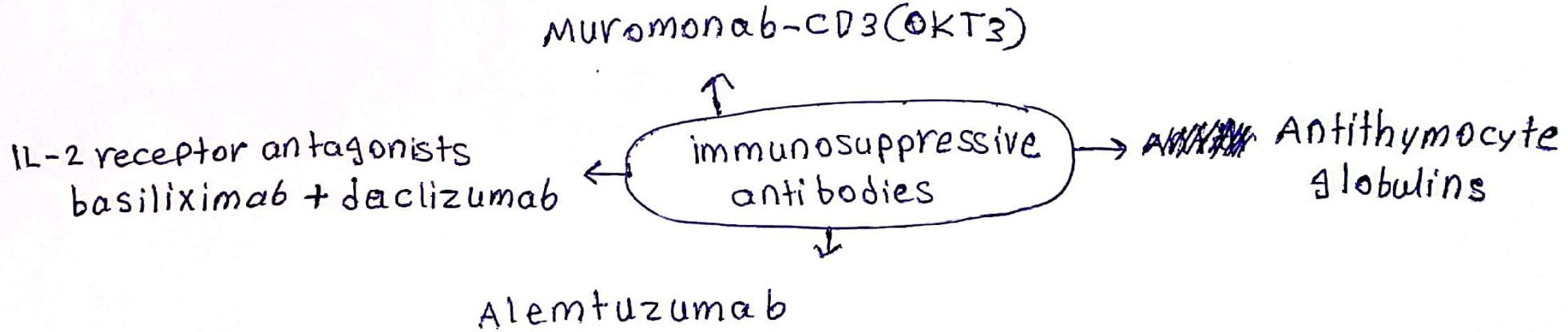
mycophenolate + antiacids (mg, AL) = decrease absorption of mycophenolate.
+ cholestyramine

* immunosuppressive according (MOA) : → interfere with cytokine.
  → disrupt cell metabolism, preventing lymphocyte proliferation.
  → mono- and polyclonal antibodies block T-cell.

* immunosuppressive drug: → severe toxicities → when used as → monotherapy.

* immune activation → three-signal model : → signal 1 : → CD3.
  → signal 2 : → CD80 + CD86.
  → signal 3 : → T-cell proliferation.

* signal 1 + signal 2 : → activate calcium-calcineurin phathway



* Antithymocyte globulins :
  - → Polyclonal antibodies
  - → used for :
    - → prevent early allograft rejection.
    - → treat severe rejection episodes.
    - → treat corticosteroid-resistant acute rejection.
  - → (MOA) : → bind the surface T-cell
    - ↓
    - Phagocytosed in the liver and spleen
    - ↓
    - Lymphopenia + impaired T-cell responses
  - → (S/E) :
    - → chills and fever.
    - → leukopenia and thrombocytopenia.
    - → infection
    - → skin rashes.

* Muromonab-CD3 (OKT3) :
  - → monoclonal antibody.
  - → (MOA) : → bind to CD3 ⇝ disruption T-cell.
  - → discontinued from market.

* Basiliximab: → anti-CD25 antibody.
→ binds to α chain IL-2 ⇝ inhibit T-cell.
→ Basiliximab + cyclosporine + corticosteroid ⟶ for prophylaxis of acute organ rejection in renal transplant
→ (S/E): ⟶ GI toxicity
→ [redacted]: ⟶ Daclizumab: ⟶ "humanized antibody"

* [redacted] Alemtuzumab: → humanized antibody
→ binds to CD52
→ treatment → B-cell chroniclymphocytic leukemia (CLL)
→ multiple sclerosis.
→ (S/E): → lymphopenic
→ neutropenic
→ anemic
→ should be closely monitored of opportunistic infection and hematologic toxicity.

* clucocorticoids:
  - first pharmacologic agents to be used as immunosuppressive
  - mainstays for attenuating rejection episodes
  - (S/E):
    - diabetogenic .
    - hypercholesterblemia .
    - cataracts .
    - osteoporosis .
    - hypertension .