بسم الله الرحمن الرحيم

Immunosuppressive drugs

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immunosuppressive drugs

- Immunosuppressive drugs are used to inhibit the immune response.
- Immunosuppressants are needed to prevent rejection of **transplanted tissues & organ** and in treating **autoimmune disease**.
- However, the **life-long use** would suppress the entire immune system exposing patients to higher risks of infections and cancers.
- Immunosuppressive drugs act through inhibiting cytokine release, inhibiting immune cell signaling, or proliferation.
- Immunosuppressive drugs include **Glucocorticoids**, **calcineurin inhibitors**, **mTOR inhibitors**, **anti-metabolites**, **biologic agents & antibodies.**

1-Corticosteroids

High doses of Glucocorticoid can cause:

1. Lysis & redistribution of lymphocytes causing rapid transient decrease in peripheral blood lymphocyte counts.
2. Down-regulation of gene expression of the pro-inflammatory cytokines such as IL-1 and IL-6
3. Inhibition of T lymphocytes and inhibit their production of IL-2.
4. Decrease the chemotactic property of neutrophils & monocytes and their lysosomal enzyme production.

- **Prednisone & methylprednisone are examples.**

- Adverse effects on long-term use: Hyperglycemia, hypertension, edema, osteoporosis, **Cushing** features, peptic ulcer, and recurrent infections.

- Glucocorticoid are used in different autoimmune diseases including immune-mediated thrombocytopenia purpura, rheumatoid arthritis, systemic lupus erythematosus, pemphigus and Crohn's disease.

- Glucocorticoid are used in Management of graft versus host disease (GvHD) which is a serious complication of allogeneic bone marrow transplants where donor lymphocytes (graft) could not self recognize the recipient's body (host).

- Glucocorticoid are used early in all solid organ transplants to prevent organ rejection.

- Glucocorticoids are used also in treatment of acute lymphoblastic leukemia.

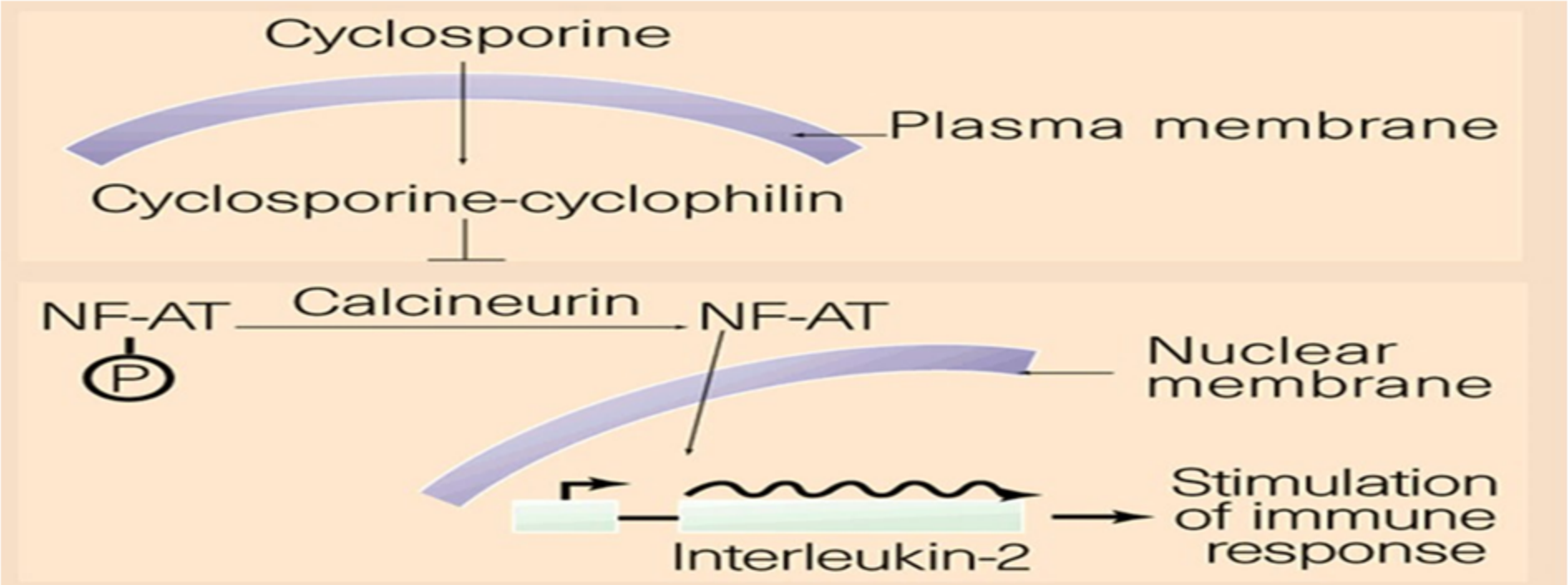
2- Calcineurin inhibitors

1-Cyclosporine A

Cyclosporine also spelled Ciclosporin, and **cyclosporin.**

- **Mechanism of actions**: **it inhibits calcineurin (a calcium-dependent phosphatase) which is needed for the activation of T- lymphocytes.**
- **Cyclosporine suppresses T- lymphocyte cell functions.**

➢ **N.B Calcineurin is critical for kidney function.**



Therapeutic uses of cyclosporine:

– Cyclosporine is the drug of choice for organ or tissue transplantation to prevent rejection reactions. IT may be used with or without other immunosuppressive drugs (+/– mycophenolate, +/– steroids, +/– cytotoxic drugs)

❑Cyclosporine is used in treating **rheumatoid arthritis, psoriasis** & other autoimmune disorders.

Side effects of cyclosporine:

1-Nephrotoxicity *2-Hypertension*

3-Hypertrichosis (hirsutism) *4-Hyperlipidemia*

5-Hyperuricemia *6- Hyperkalemia*

7- Gum hyperplasia. *8-Drug interactions*

9-Increase risk of secondary tumors (especially lymphoma) and opportunistic infection (Fungal, bacterial, etc.)

Cyclosporine is safe during pregnancy (Category C).

Drug interactions of cyclosporine

- Verapamil, ketoconazole, erythromycin and Glucocorticoids inhibit CYP3A4 and increase blood level of cyclosporine.
- In contrast, drugs that induce CYP3A4 lower blood level of cyclosporine like phenytoin and rifampin.
- Cyclosporine needs **therapeutic drug monitoring**.

2- Tacrolimus

Mechanism: it inhibits calcineurin as cyclosporine, but tacrolimus is 10–100 times more potent than cyclosporine.

It is used **oral** or **IV.** Half life is about 9 – 12 hours.

Therapeutic uses:

- Tacrolimus is used to prevent rejection after organ transplantation.
- Topically, Tacrolimus is used in treatment of **vitiligo** and various inflammatory and allergic skin diseases (like atopic dermatitis).

Side effects of tacrolimus:

1- Nephrotoxicity 2- Hypertension 3- Hyperkalemia

4-Increase risk of secondary tumors and opportunistic infection

5-Neurotoxicity (tremor & seizure)

6-Hyperglycemia & diabetes.

7-If given with mycophenolate, diarrhea and alopecia are common.

3- Antimetabolites and cytotoxic drugs

1-Mycophenolate mofetil

- It is converted to the active form (Mycophenolic acid) which **inhibits inosine monophosphate dehydrogenase** (IMPDH), leading to inhibition of *de novo* purine synthesis & suppression of T and B lymphocyte proliferation.
- It is used after **organ transplantation** & for treating **autoimmune disease**.
- Adverse effects: Hepatotoxicity, infections & **bone marrow depression**.
- **It is contraindicated during pregnancy.**
- **It is used as adjunctive therapy after organ transplantation to permit dose reduction of cyclosporine.**

2- Azathioprine

- It is a pro-drug to 6-mercaptopurine **(6-MP)** which inhibits purine synthesis (↓ proliferation of lymphocytes).
- Azathioprine is used in organ transplantation, severe rheumatoid arthritis, inflammatory bowel disease & other autoimmune disease.
- **6-MP is used in childhood Acute lymphoblastic leukemia.**

3- Cyclophosphamide

- It is an alkylating agent that can **disrupt DNA** and decrease the number of lymphocytes and hence decrease the production of autoantibodies.
- The major adverse effect is bone marrow suppression.
- **Cyclophosphamide is contraindicated during pregnancy.**

4-Leflunomide

- It inhibits pyrimidine synthesis leading to suppression of immune cells.
- It is widely used for treating autoimmune diseases.

Adverse effects: **Diarrhea** (common) and hepatotoxicity.

It is contraindicated during pregnancy.

3- mTOR inhibitors

Sirolimus (rapamycin) & everolimus.

- They are **not calcineurin inhibitors** and little nephrotoxicity occur.
- They are proliferation signal inhibitors.
- They block the **molecular target of rapamycin (mTOR).**
- They inhibit T-cell & B-cell proliferation and ↓ immunoglobulin production.

Pharmacokinetics:

- Sirolimus is available as an **oral drug**. Its half-life is about 60 hours.
- Metabolized by cytochrome P450 and excreted via P-glycoprotein.
- Significant drug interactions can occur and **Monitoring is** needed.

Toxicity:

1- Profound myelosuppression (especially thrombocytopenia).
2-Hepatotoxicity.
3-Diarrhea.
4-Hypertriglyceridemia.
5- Pneumonitis and headache.

Therapeutic uses

1- Sirolimus has been used alone and in combination with other drugs to prevent rejection of solid organ allograft.

2- Topical sirolimus is used in some dermatologic and occular disorders. E.g. Sirolimus plus cyclosporine is used in the management of uveoretinitis.

3- Recently, **sirolimus** eluting coronary stents have been shown to reduce re-stenosis (due to Antiproliferative effects) in patients with severe coronary artery disease.

4- Sirolimus eluting stent (SES) for **Eustachian tube dysfunction** to suppresse stent-induced tissue hyperplasia.

4- Biological immunosuppressive drugs

➢ **Muromonab** (CD3 blocker) was the first monoclonal antibody approved for humans (1986), designed to treat acute organ transplant rejection. it was voluntarily withdrawn.

➢ *T-cell inhibitors: Basiliximab (anti-IL-2 receptor antibodies) to prevent acute rejection of transplanted organs.*

➢ *B-cell depleting agents: Rituximab (Anti CD 20) treats certain cancers (Non-Hodgkin Lymphoma, Chronic Lymphocytic Leukemia) and autoimmune diseases (rheumatoid arthritis, pemphigus vulgaris)*

➢ *TNF-alpha inhibitors: Adalimumab , Infliximab for treating autoimmune disease*

➢ *Janus Kinase (JAK) Inhibitors: Tofacitinib for certain autoimmune diseases.*

5- Polyclonal immunosuppressive antibodies

1- Antithymocyte globulin (ATG or ATGAM).

ATG is a purified γ-globulin from serum of rabbits immunized with human thymocytes. ATG has a direct cytotoxicity to lymphocytes

2- Thymoglobulin

Polyclonal antibodies targeting B & T lymphocyte, natural killer cell & plasma cell surface antigens. It induces rapid apoptosis of CD3+ T cells present in the bloodstream.

➢ Both ATG and thymoglobulin are indicated in acute renal transplant rejection in combination with other immunosuppressive agents.

Rh (D) Immune Globulin

Rho (D) immune globulin is a concentrated (15%) solution of human IgG containing antibodies against the Rho (D) antigen of the red blood corpuscles.

It is administered to the Rh negative mother within 24–72 hours of Rh+ delivery or abortion (to destroy any fetal Rh-positive RBCs in the mother's blood before the generation of maternal B-cell response against fetal Rh+ RBCs)

This could inhibit the potential hemolytic anemia (hemolytic disease of the newborn) in the next baby.

Rh-negative woman

Rh-positive foetus

Maternal isoimmunisation

Immune Globulin Intravenous (IGIV or IVIG)

This immunoglobulin preparation (usually IgG) is prepared from pools of thousands of healthy donors, and no single, specific antigen is the target of the "therapeutic antibody."

Possible mechanisms of action of IGIV include:

1- Reduction of T helper cells.
2-Decreased spontaneous immunoglobulin production.
3- Fc receptor blockade.
4- Increased antibody catabolism.
5- An interaction with "pathologic antibodies."

- **IVIG does not increase the risk for infection**.
- IVIG is considered **safe for use during pregnancy and breastfeeding**.

Therapeutic uses of IGIV:

1- As a replacement therapy in immunodeficiency (e.g. after bone marrow transplantation and HIV). Low dose (400 to 600 mg/kg per month).

2-High doses (1-3 g/kg) is effective in a variety of autoimmune disorders:

A. **Kawasaki** disease (preventing coronary artery aneurysms)
B. immune-mediated thrombocytopenia purpura (**ITP**)
C. **Guillain-Barre syndrome**
D. Systemic **Lupus erythomatosus.**
E. Myositis, **dermatomyositis**.
F. Neurological diseases like **myasthenia gravis** or **multiple sclerosis.**
G. **Toxic epidermolytic necrolysis.**

3- As a **hyper-immune therapy** against specific **infectious agents.**

Adverse effects:

Common: headache, erythema, **vomiting**, myalgia, and **fever**.

Uncommon and rare: Anaphylaxis, Aseptic meningitis, acute renal failure, arrhythmias, lung injures, and dermatological manifestations.

✓Adverse effects are preventable with certain pre-medications, including non-steroidal anti-inflammatory drugs, antihistamines, corticosteroids, or saline for pre-hydration.


Thank you!