بسم الله الرحمن الرحيم

Lecture pharmacology

immunomodulatory drugs

By
Dr. Mohammad Salem Hareedy
2024

ILOS

By the end of this lecture, you should be able to:

1-Recognize the major mechanisms of action of Immunosuppressive drugs.

2-List the toxic manifestations of Immunosuppressive drugs.

3-Mention the major therapeutic uses of Immunosuppressive & immunostimulant drugs.

4-Identify the important drug interactions of Immunosuppressive drugs.

1- Immunosuppressive drugs

- Immunosuppressive drugs are used to inhibit the immune response.

- This immunosuppressant effect is needed to prevent rejection of **transplanted tissues & organ** and in treating **autoimmune disease**.

- However, such therapies require **life-long use** and nonspecifically suppress the entire immune system exposing patients to higher risks of infections and cancers.

1-Corticosteroids

The immunosuppressive action is mediated through the Glucocorticoid effects:

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

- **Prednisone and methylprednisone are examples.**

- **Adverse effects: Hyperglycemia, hypertension, edema, Cushing features, peptic ulcer, and recurrent infections.**

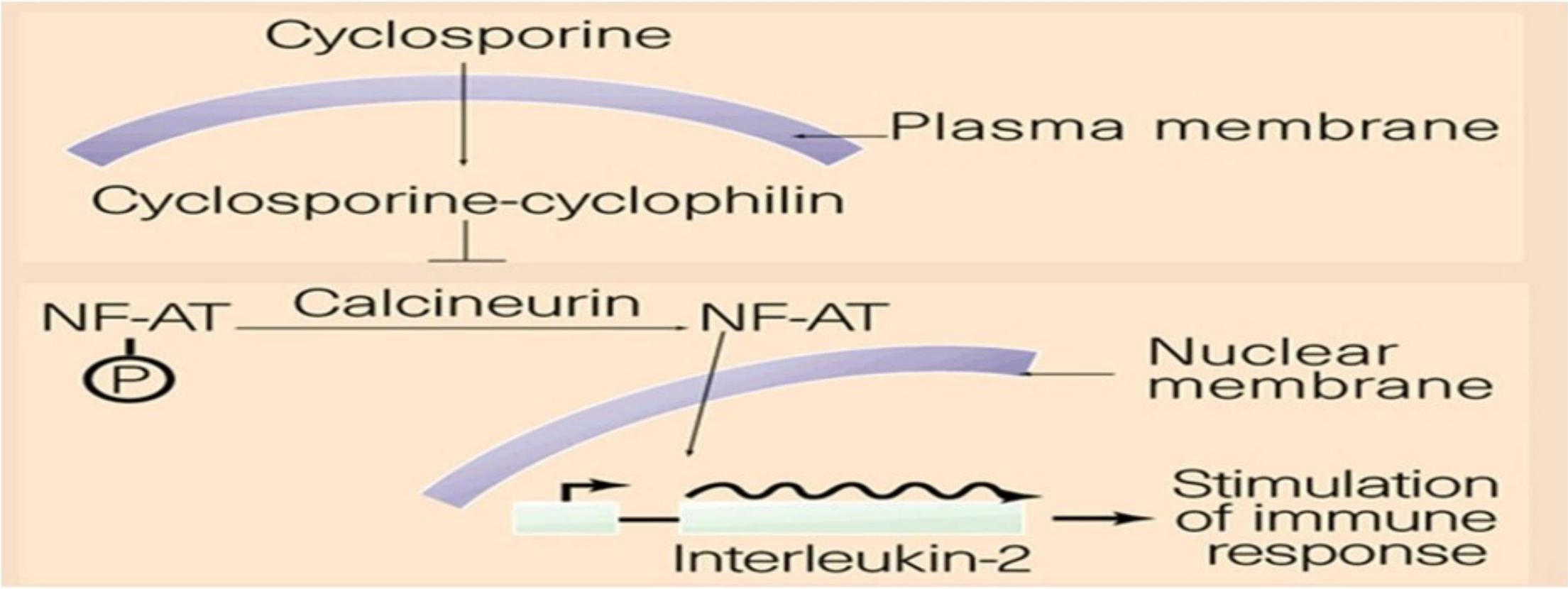
2- Calcineurin inhibitors

1-Cyclosporine A

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

Mechanism : it inhibits calcineurin which is needed for the activation of T- lymphocytes. So, Cyclosporine suppresses T-cell functions.

- **T- lymphocyte inactivation will decrease interleukin2 formation inside T- lymphocytes.**



Therapeutic uses of cyclosporine:

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

– 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)

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

- Drugs that inhibit CYP3A4 will increase blood level of cyclosporine like verapamil, ketoconazole, erythromycin and glucocorticoids.
- 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:

1. Tacrolimus is used like cyclosporine as an anti-rejection in organ transplantation.
2. 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 and 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 which inhibits purine synthesis. This would block the proliferation and functions of lymphocytes. As immunosuppressive, it is used in organ transplantation as well as severe rheumatoid arthritis.

3- Cyclophosphamide

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

4-Leflunomide

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

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

It is contraindicated during pregnancy.

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 both 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 3A 4 and excreted via P-glycoprotein.

Hence, significant drug interactions can occur and need **Monitoring**.

Toxicity:

1- Severe bone marrow depression (especially thrombocytopenia).

2-Hepatotoxicity.

3-Diarrhea.

4-Hypertriglyceridemia.

5- Pneumonitis, and headache.

Therapeutic uses of mTOR inhibitors.

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

2- Topical sirolimus is also used in some dermatologic disorders and, in combination with cyclosporine, in the management of uveoretinitis.

3- Recently, **sirolimus** eluting coronary stents have been shown to reduce re-stenosis & additional adverse cardiac events in patients with severe coronary artery disease, due to the drug's Antiproliferative effects.

Biological immunosuppressive drugs

Examples:

1- Interleukin-2 (IL-2) antibodies (Daclizumab & Basiliximab) and muromunab-CD3 to prevent acute rejection.

2- TNF-a inhibitors (Etanercept and Infliximab) for treating autoimmune diseases like rheumatoid arthritis.

Polyclonal immunosuppressive drugs

1- Anti-thymocyte globulin (ATG or ATGAM).

ATG is a purified gamma globulin from the serum of rabbits immunized with human thymocytes. ATC has direct cytotoxicity to lymphocytes.

2- Thymoglobulin

Polyclonal antibodies targeting B and T cells, natural killer cell & plasma cells surface antigens. It induces rapid apoptosis of CD3+ T cells.

✓ Both are indicated in **acute** renal transplant rejection.

Anti-D immunoglobulin

- **Human IgG** Ab against red blood cell D (rhesus) antigen.
- It is **injected** to Rh-negative mother within 72 h of Rh+ delivery or abortion (to destroy any fetal Rh+ RBCs in the mother's blood before the mother can generate a B-cell response against fetal Rh+ RBCs), this would prevent the potential hemolytic disease in the next baby.

Immune Globulin Intravenous (IGIV or IVIG)

An immunoglobulin preparation (usually IgG) prepared from pools of thousands of healthy donors, and no single, specific antigen is a target of IGIV.

Although the precise mechanism of action is still unknown, IGIV can produce:

1- Reduction of T helper cells.

2-Decreased spontaneous immunoglobulin production.

3- Fc receptor blockade.

4- Increased antibody catabolism.

5- An interactions 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 several autoimmune & inflammatory disorders:

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

2- Immunostimulant agents

Definition:

Immunostimulant agents are substances (drugs and nutrients) that stimulate & increase the activity the immune system.

Value:

Immunostimulants can enhance body's resistance against various infections & cancers.

Examples:

1- Vaccines and specific immunoglobulins.

2- Natural and herbal supplements like echinacea.

3- Cytokines like interferons and interleukins.

4-Drugs like thalidomide (immunomodulator agent), levamisole.

Examples of Immunostimulants

1-Bacillus Calmette- Guerin (BCG vaccine)

Mechanism: Enhancement of B and T cell-mediated responses.

Therapeutic uses:

1- Vaccination against T.B.

2- Prophylaxis and treatment of urinary bladder carcinoma.

Side effects: Hypersensitivity, shock, chills, fever, & malaise.

2- Thalidomide

Uses: treatment of multiple myeloma and leprotic reactions.

Adverse effects: Teratogenicity (Phocomelia).

3- Levamisole: used in treating colon cancer and immunodeficiency in Hodgkin's lymphoma.


Thank you!