SHEET NO. 25

# IMMUNOLOGY

## DOCTOR 2019 | MEDICINE | JU


DONE BY : Sohib Al-Shabatat

SCIENTIFIC CORRECTION : Sohib Al-Shabatat

GRAMMATICAL CORRECTION : Sohib Al-Shabatat

DOCTOR : Malek Zehlif

# Immuno pharmacology

*الكلام بالأسود شرح الدكتور, والملون كلام السلايدات..

*الشيت سهل ان شاء الله,, موفقين

💙

---

🧠 Immune system has an important function of protecting our body, however, sometimes it goes in another way of working and become harmful to the host, this harm come from what we called exaggeration in immune system response.

=e.g: Sepsis; when bacteria reaches the blood, our immune system response become enormous.

=e.g: COVID-19; some people their immune system response in a proper way they recover 😜 بينشفوا, however, those who response in an exaggerated way they develop cytokine storm and this make a state of instability in the body so our body attack lung cells and that what kill them.

**another example is autoimmune diseases, such as: Rheumatoid arthritis (immune cells attack joints), Systemic Lupus Erythematosus, Psoriasis الصدفية, Inflammatory bowel disease (IBD),, all these disease result from exaggeration in immune response.

🧠The role of pharmacology in this field is to increase or decrease the immune response using drugs, so we should be precise to avoid any problem.

🧠 When we use immuno pharmacology?

**Agents that modulate the immune system play an important role in:

1. Preventing the rejection of organ or tissue grafts (as the rejection made by T cells toward transplanted organ, we need to inhibit it)
2. In the treatment of certain diseases that arise from dysregulation of the immune response.

•Autoimmune diseases.

•Immunodeficiency diseases.

➔So in this cases we need to make treatments to these diseases.

## Solid Organ and Bone Marrow transplantation

*when we transplant an organ (kidney for example) we will face rejection by the immune system of the patient, this rejection comes in four types:

**-hyper-acute (the rejection occur directly after you put the kidney).**
**-accelerated (immune attack occur within days).**
**-acute (occur within months of transplantation).**
**-chronic (occur within years).**

*What we need to do is to prevent the chronic and acute rejection, other types are hard to deal with.

Now the idea is: transplant of organ introduces foreign tissue to the body, the body's immune system sees this foreign tissue, thinks it's bad and start producing lymphokines including **IL-2,** the lymphokines then activates the immune system even further, leading to a nasty cycle of foreign tissue destruction rejection.

-IL-2 do migration of immune system cells, and when activated cells arrive, they activate more immune cells, this lead to exaggeration which attack the transplanted organ and destroy it; so we need to inhibit the immune system.

important note: there is NOT two patients have the same MHC (or the same antigens) even if they are identical twins, identical twins DNA differ in the area which is responsible of immune genes (so there's rejection of transplantation between them).

The drugs we use to inhibit the immune system are called Transplant Rejection agents.

transplant rejection agents are **narrow spectrum agents** so we need special way to deal with them.

*Many problems exist in currently approved regimens أنظمة:

1. Treatments are often very complex: we need to use many drugs.
2. low patient compliance: patient don't **adhere to medication**, because it cause toxicity and used for long period of time.
3. Therapeutic margins (or therapeutic index) can be very narrow.
4. Pharmacokinetic interaction potential is high and causes problems: these drugs interact with other drugs in very very complex way.

Unfortunately, these agents also have the potential to cause disease and to increase the risk of infection and malignancies.

=when we transplant any organ (heart, kidney, lung…etc) we need to do all possible ways to inhibit immune rejection, this mean that we need to control all ways that activate the immune system, so we do combination of drugs with different mechanisms of action and different toxicity BUT as we say these drugs are used for years maybe 4 or 5 with average of 3 years, and have narrow therapeutic window so the patient must take them in time to avoid over toxicity (on the kidney) or under activity (means there is rejection).
*Moreover, these drugs are metabolised by cytochrome P450, so it may interact with other drugs if taken together which cause increase or decrease of their concentration in the blood.

you may notice that the use of these drugs for years make the patient immunocompromised which make him susceptible to infections so we should isolate him, another thing that he could develop cancer.
المسكين بيجيها يمين بتيجيه شمال بيجيها شمال بتيجيه يمين

## The Drugs That We Use:

-Glucocorticoids (or glococorticosteroid) which is the cortisone.
- Calcineurin inhibitors such as: Cyclosporin A & Tacrolimus.
-Anti-metabolites such as: Azathioprine, Mycophenolates &Leflunomide: we talk about them in cancer lectures specially 5-florouracil when we talk about colon cancer, we said that it enters the DNA and inhibit transcription because it produces false nucleotide.
-IL-2 receptor 'mabs' they block IL-2 reseptor, such as: Basiliximab & Daclizumab: these new drugs we call them Biologics, which means that its designed to bind to specific locations within the body and not affect all the body.
-m-TOR inhibitors (m-TOR is a protein responsible of cell cycle) such as: Sirolimus, so we stop immune cell proliferation between G1 and S phase by inhibiting m-TOR.

# Glococorticoids

They are core drugs in treatment of these patient that are transplanting organs.
Glucocorticoids suppress the cell mediated immunity (T cells immunity) Inhibiting genes that code for the cytokines, the most important of which is IL-2 and sometimes IL-1 (intercellular drug).

*remember that IL-1 is important in activation and migration of T-cells.

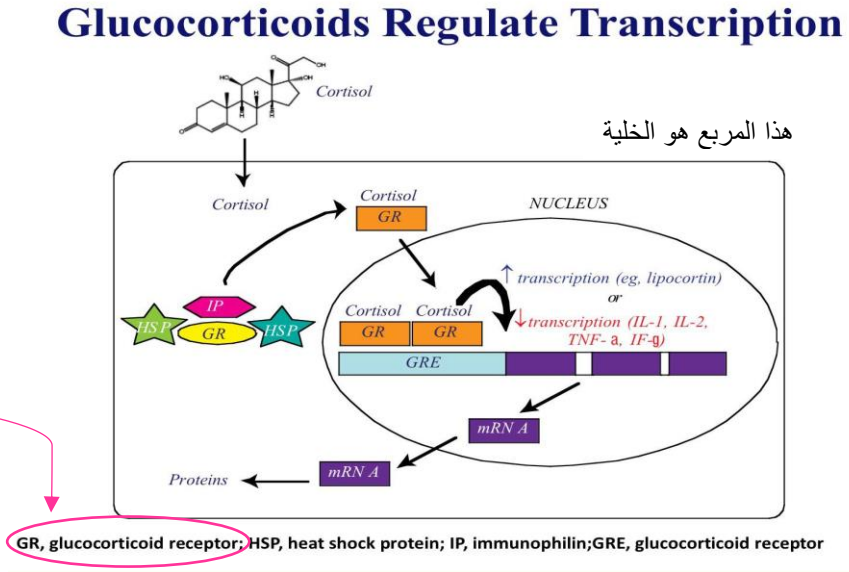
★Smaller cytokine production reduces the T cell proliferation.

★Glucocorticoids also suppress the humoral immunity, causing B cells to express smaller amounts of IL-2 and IL-2 receptors.

֍ Cellular immunity is more affected than humoral immunity because smaller doses will affect cellular immunity.

★ Glucocorticoids are also anti-inflammatory drugs (they are the strongest anti-inflammatory drugs), so we will use it in lots of cases (its magical drug).

= in treatment of any inflammation we start by giving glucocorticoids, e.g: asthma patient: they have inflammation in trachea and bronchi, so we use this drug with other drugs as a mixture in the Symbicort البخاخ this Symbicort has: long acting β2 agonist (LABA) + glucocorticosteroid.




֍ look at the picture... Cortisol (which is found in our bodies) cross the cell membrane, then it binds to its receptor inside the cell,, then this complex (GR) enter the nucleus, then it bind to glucocorticosteroid receptor element (GRE) which found in the promoter region of many many genes (nearly quarter of the genes),,it induce some of them and inhibit the other; inhibit transcription of (IL-1, IL-2,TNF- a, IFN- g) which are responsible of T cell activation so it inhibit cellular immunity which is responsible of rejection, & increase transcription of (lipocortin) which has anti-inflammatory effect (by this glucocorticoids has anti-inflammatory effect).

★Clinically:

֍ Glucocorticoids are first-line immunosuppressive therapy for both solid organ (kidney, liver, heart, lung) and hematopoietic stem cell transplant recipients (bone-marrow transplant) and graft-versus-host disease(GVHD) (immune cells that come with the transplanted organ and attack the host cells such in cornea transplant).

تعريف ال GVHD مهم جداً

idiopathic بدون سبب thrombocytopenic purpura and rheumatoid arthritis.

(thrombocytopenic نقص حاد في عدد الصفائح الدموية ) (purpura -from google: a rash of purple spots on the skin caused by internal bleeding from small blood vessels).

=this happen because the immune system is destroying platelets so we use the drug to avoid this reaction.

=in rheumatoid arthritis the immune cells attack the joints, so we also use glucocorticoids to avoid this reaction.

Glucocorticoids modulate allergic reactions and are useful in the treatment of diseases like asthma (to reduce the inflammation and the allergy) or as premedication for other agents (eg: blood products) that might cause undesirable immune responses.

-Glucocorticoids are the best anti-allergic drugs ever.

## ★ Side Effects of Glucocorticosteroids:

*before we transplant the organ we give the patient high dose of methylprednisolone 500 mg intravenously (IV and sometimes IM) to shut the immune system down, after transplantation we give the patient 20 mg daily for 6 months and we start to reduce the dose for another 6 months.

⇨ methylprednisolone is a synthesised glucocorticoid ⇦

1} Immunodeficiency

2} Adrenal glands will stop synthesise glucocorticoids because we give it externally so it will atrophies يضمر, to avoid this we start lowering the dose after 6 months.

3} Hyperglycemia because it increases the gluconeogenesis,, and Fat redistribution around the face and the neck (moon face and buffalo hump), because genes that are responsible for fat distribution are changed by using this drug.

4} Growth failure, delayed puberty.

5} Excitatory effect on central nervous system (euphoria زهزهة, psychosis):it enters the brain because its lipophilic.

6} Osteoporosis هشاشة عظام : because its reduces calcium deposition and increase the activity of osteoclast over the osteoblast if it used for more than 6 months so we use it just for 6 months. الدكتور ركز عالمدة كثير

7} Cataracts: increase the ocular presser إعتام عدسة العين

8} Gastric ulcers: (prevent with drugs that reduce the acidity such as: omeprazole, misoprostol) حفظ مش هذول الأدوية

9} hypertension.

so this drug affects all the body because it affect the gene expression of more than 20% of our genes. رغم كل هالمصايب مجبورين نعطيه لانو فش غيره

# Calcineurin Inhibitors Cyclosporine & Tacrolimus

## Clinical Uses:

A] human organ transplantation.

B] graft-versus-host disease after hematopoietic stem cell transplantation: to avoid the transplanted stem cells (which develops to become immune cells) from attacking the patient body.

C] selected autoimmune disorders.

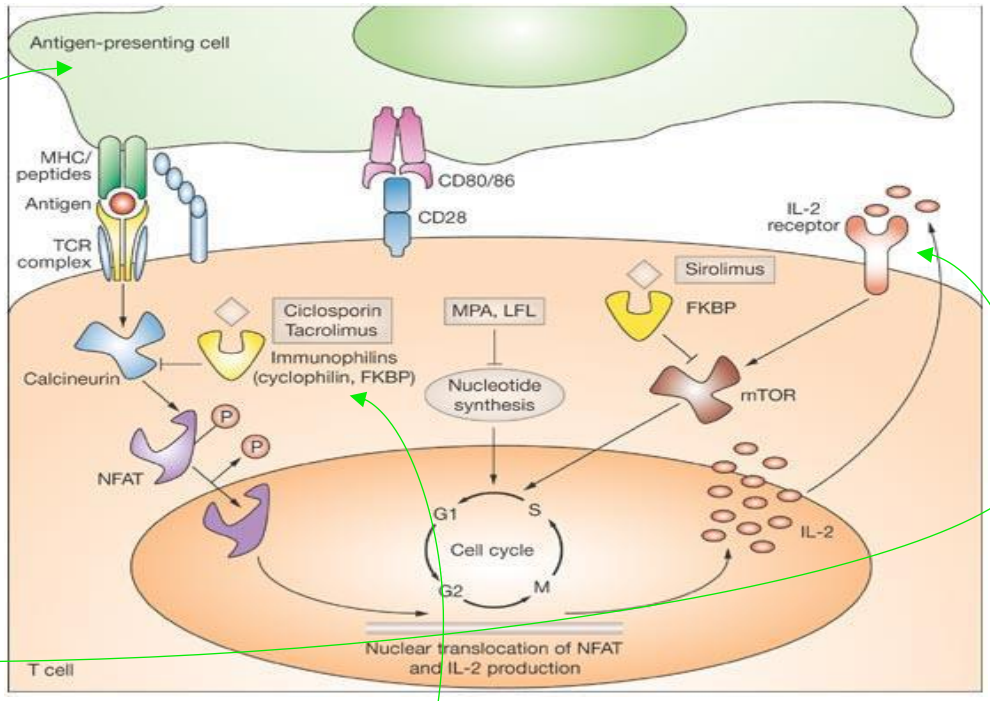
## Mechanism of action:

Both Inhibit the cytoplasmic phosphatase (so they are intercellular drugs), calcineurin, which is necessary for the activation of a T-cell-specific transcription factor.

This transcription factor,NF-AT, is involved in the synthesis of interleukins (eg,IL-2) by activated T-cells.

So these drugs will affect indirectly the gene expression so its effect is less than glucocorticoid (because it has direct effect).

Look at the figure -as we see APC will activate T- cell by MHC binding to TCR which activates calcineurin, calcineurin as a phosphatase it dephosphorylates NFAT which in turn inter the nucleus and increase the expression of IL-2, IL-2 exit the cell and bind to its receptor on the cell surface (autocrine) which increase the activation and migration of T-cells.




our drugs in the cell bind to immnuophilins which has 2 types (cyclophilin which bind cyclosporine, FKBP which bind tacrolimus), now immunophilin when activated it inhibits calcineurin which in turn inhibit IL-2 and T-cell activation.

## Complexity:

- metabolized by the P450 3A (CYP 3A4, CYP 3A5) enzyme system in the liver with resultant multiple drug interactions.

=Any drug inhibits CYP 3A4 or CYP 3A5 will increase the concentration of Cyclosporine & Tacrolimus in the blood (drug-drug interaction).

IMPORTANT: CYP 3A4 and CYP 3A5 are polymorphic (has SNP single nucleotide polymorphism) which means that everyone has different activity of them, some patient are poor metabolisers and some are intermediate metabolisers and some are fast metabolisers and some are ultra-rapid-metabolisers,, so depending on the phenotype we determine the concentration in the patient's blood.

- Narrow therapeutic window

=Levels too high: toxicities (i.e. nephrotoxicity in kidney transplantation, mental confusion, hyperglycemia and hypertension)

=Levels too low: transplant rejection.

- Increased incidence of lymphoma and other cancers (Kaposi's sarcoma, skin cancer) have been observed in transplant recipients receiving cyclosporine.

## Target drug monitoring:

- cyclosporine is one of the drugs that we monitor it, we must determine it's concentration in the blood, so we should monitor:

>Cyclosporine trough قاع levels: we need to determine the lowest concentration of the drug after the first dose and before we give him the second dose, to know how much of it still in the blood

>Serum electrolytes: to make sure that it doesn't cause kidney toxicity because it affects their concentration in the blood.

>Renal function (because it causes renal toxicity).

>Hepatic function: because it also affects the liver (hepatotoxicity).

>Blood pressure: because it increases the blood pressure.

>serum cholesterol: because it increases the lipid amount in the body.

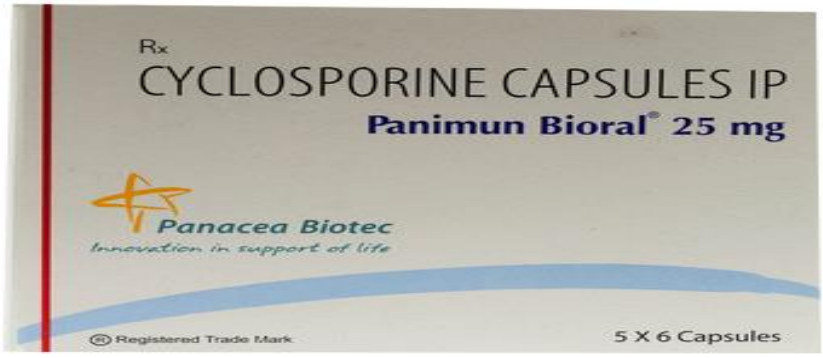
## Another Uses:

- Cyclosporine ophthalmic solution قطرة العين is now available for severe dry eye syndrome (the immune system attack the eye and cause sever dryness), as well as ocular graft-versus-host disease GVHD.
- In combination with methotrexate, cyclosporine is a standard prophylactic regimen to prevent graft-versus-host disease after allogeneic stem cell transplantation.

Cyclosporine has also proved useful in a variety of auto-immune disorders, including uveitis التهاب القزحية rheumatoid arthritis, psoriasis الصدفية, and asthma.

## Tacrolimus:

the same thing as cyclosporine, but it has low toxicity on the kidney so nowadays we prefer to use it BUT remember we should do blood monitoring (remember, it has narrow therapeutic window).
= it can cause Diabetes mellitus.




وهي أحلى صفحة فاضية
عشان تدعولي
وتسامحوني عالشيت المدحش حكي