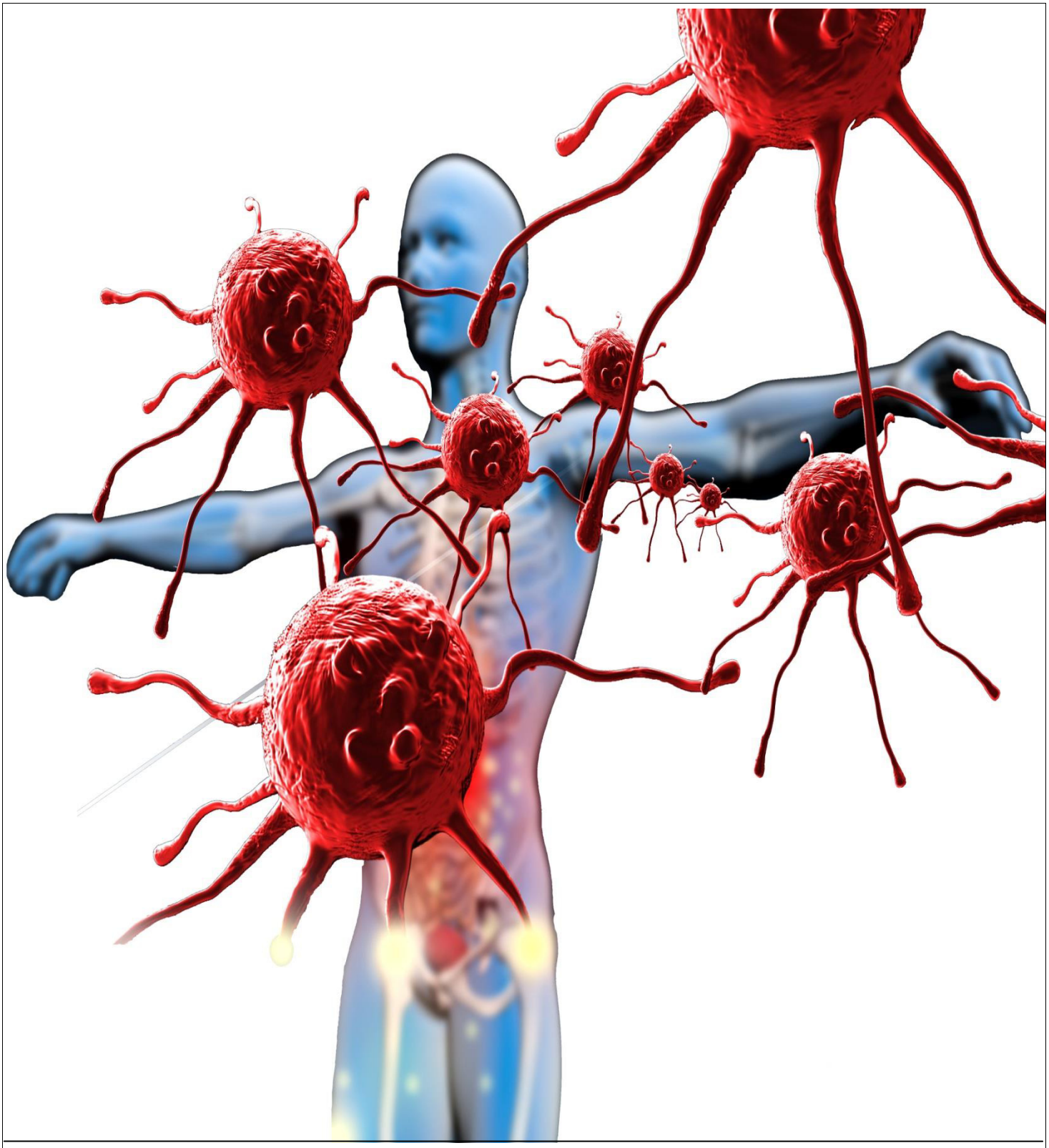


IMMUNOLOGY

Done By: Ola Atif

#22

Dr. Malik Zihlif

By Mohammed Nawaiseh

IMMUNOPHARMACOLOGY

Introduction:

We will take an overview of something very complex which is immunopharmacology.

The most difficult thing in pharmacology is to deal with anticancer drugs and immune modulators because they are really toxic drugs, no jokes with such drugs, you have to work with them very closely, you can't give them to a patient then send him home. With using these drugs you should monitor your patient.

So immune pharmacology is critical to deal with even the patient is going to suffer from them, because we are interventing with one of the core stones of the body of a patient (the immune system).

If you decrease the immunity generally you get your patient more toward infections, cancer and problems.However, increasing the immunity is not something very simple because you make your patient's body recognize something familiar as a foreign material.
So you are standingin the middle which is a narrow area.

The best examples of narrow therapeutic index to deal with are**immunosuppressants**

We are going to talk about things within the immune system : either

1. **In treating an autoimmune disease** where the patient has increased unwanted immunity where the patient's immunity is reacting toward his body and this is something you don't want, like: ulcerative colitis, lupus and rheumatoid arthritis.
2. **In transplanting an organ** (kidney, heart or lung) and you don't want the body to have a good immunity now.

Written by Ola Atif

On the other hand, in many cases we have reduction in immunity and we want to increase it, mostly **in cancer** we use immunomodulators, especially immunotherapy is becoming very popular. Last year a drug was approved and this year other 2 drugs will be approved, these drugs mostly work on **IBD**"Inflammatory Bowel Disease".

Where do we use immune pharmacology?

1- Agents that modulate the immune system, they play an important role in **preventing rejection of organs or tissue transplantation** (the topic of this lecture)

2- **Treatment of certain diseases**that arise from dysregulation of immune response by autoimmune disease or immunity deficiency diseases. (the topic of the next lecture)

Organ transplantation is one of the most complex things to do in this life, it is not simple. **Rejection is going to happen unless the donor and recipient are identical twins**, so what we are going to do is to **delay this rejection** or **prevent it.**

On reality, we can't prevent the rejection 100%, in the best cases we prevent it by **46-50% in kidney transplantation**.
So**what we do is delaying this rejection** but at the end of the day we will end up with rejection.

The rate of rejection is high in heart transplantation, higher in lung transplantation, but less in kidney transplantation
(rate of rejection: lung > heart > kidney)
We will talk about the best example which is kidney transplantation.

We have 4 types of rejection that can occur in organ transplantation:
1- Hyperacute
2- Accelerated
3- Acute
4- Chronic

Hyperacute and accelerated rejection are happening while transplanting, they result in stenosis and blockage of vessels. So you will know that the patient won't take that organ and stop the whole process of transplantation or if you complete the transplantation the organ won't stay effective in the body for a long time and you have to transplant again.

In immune pharmacology we will deal with **acute and chronic rejection**.
Acute rejection happens from **day 1 up to 3 months**.
Chronic rejection happens **after years**, maybe 2 or 3 years.

In reality we have chances of rejection either it is acute or chronic, so we will reduce the immunity by **using drugsfor very long time** (minimum 2-3 years)

These drugs have very narrow therapeutic index such as:**cephalosporins, tacrolimus, bad steroids, and sirolimus.**
You may use **anti-bodies** and **anti-cancer drugs at low doses as immune modulator.**

We won't talk deeply about immunosuppressants, it is more related to pharmD **:D**

Transplant oforgans introduces foreign tissues to the body's immune system, it sees this foreign tissue as a bad thing and starts producing lymphokines including **IL-2** and **lymphokines that activate the immune system**and can further lead to nasty cycle of foreign tissue destruction and rejection and this is what you don't want.
To reduce this, we use what we call**Immunosuppressant**

Immunosuppressant for 2-3 yearsis very complex

The story of **complexity** comes from that **1 agent is not enough to produce immunosuppression**, and because **it has so many side effects** and **you can't increase the dose of that drug** (remember it has very narrow therapeutic index), **so we combine different kinds of drugs with different toxicities** in order to have good immunosuppression.

Another story about **low patient's compliance**, we talked about it in the beginning of pharmacology last year. Because the patient is going to take the drug for years, compliance is very important.

Pharmacokinetic interaction potential is high and causes problems, this is a big issue.

Unfortunately these agents also **have potential to cause disease and increase the risk of functional malignancies** and this is the worst thing to happen.
For example: your patient had a kidney transplant, and you aregiving him immunosuppressant, the immunity is going down in his body, and he ends up with skin cancer or leukemia or lymphoma !

Groups of immunosuppressant

1- Glucocorticoids

They're the best drugsever as anti-inflammatory drugs, the magical drugs we love and hate at the same time.They're used in dermatology, respiratory, cardiologyand nephrology.They have many side effects especially when used for a long time.

As we took in pharmacology of Respiratory system ☺ steroids are the main drug to treat asthma, allergic rhinitis and allergic reactions with respiratory tract.

They are also the main drugs used by dermatologists.

Corticosteroids have 2 effects:

A) **immunosuppressant** at **high doses**
B) **anti-inflammatory** at **low doses**

2-Calcinurin inhibitors (cephalosporine, tacrolimus)

3-IL-2 receptor monoclonal anti-bodies(Daclizumab, basiliximab)

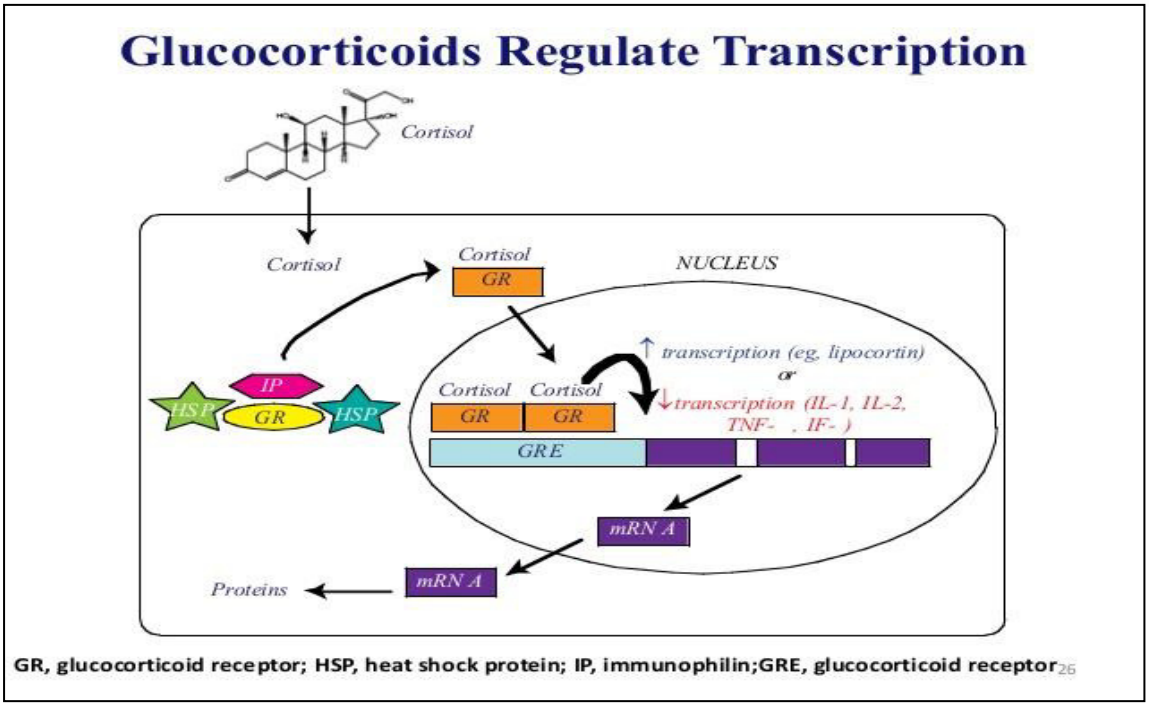
4- Anti-metabolites (anti-cancer"one of them is 6-Mercaptopurine"**, we talked about them last year)**

5-mTOR inhibitors (Sirolimus)

We will combine these drugs in many cases, to delay the rejection of transplantation.

Glucocorticoids :

- First, the doctor reads from the slide, then he clarifies: "glucocorticosteroids arrest the cell mediated immunity, inhibiting the gene that codes for cytokines, the most important of which is IL-6"



- Any steroid drug/agent**(cortisone, prednisone, methyprednisone, dexametasone)** works in this way :
  They go inside the cell, crossing the membrane and binding to their intracellular receptor**(glucocorticosteroid receptor "GR"),** this binding forms a complex, this complex goes to the nucleus, the nucleus is the machinery responsible for either replication or transcription. **Here we will affect the transcription,** so the complex inside the nucleus will bind to **(glucocorticosteroid receptor element "GRE")**foundon the DNA.
- This binding will cause:
  1- **Decrease the expression of transcription factors (IL-1, IL-2, IL-3, IL-4)**

  2- **Increase transcription of lipocortin**, which is an important component in anti-inflammatory.

  - Let's talk about lipocortin:
    Phospholipase A2 takes a lipid from the cell membrane forming **arachidonic acid**, which will form inflammatory agents/mediators**(prostaglandins, prostacyclins and leukotrienes) by COX1 and COX2**.
    Lipocortin will bindto phospholipase A2 inhibiting the process of

building the inflammatory agents (prostaglandins, prostacyclins and leukotrienes).

To sum up:

Glucocorticosteroids→ cross the cell membrane →binds to "GR" in the cytoplasm → forming a complex →the complex goes to the nucleus(DNA)→it binds to "GRE"→inhibit the immunity factors (mainly IL-2) →by this <u>we inhibit the CELLULAR IMMUNITY</u>.

- Steroids have 2 effects :
  1-Anti-inflammatory at **low dose**(throughlipocortin)
  2- Immunosuppressant at **high doses**(we still have some anti-inflammatory effect)**,** it is T-cell suppression, because IL-2 is responsible for the cycle of T-cell activation, so inhibiting it means inhibiting T-cell activation.

Normally : (as we know from immunology):

APC has MHC molecule ~~will~~ bind to TCR on T-cells ~~forming~~ a complex cascade of reactions ~~end~~ up with activation of IL-2 ~~this~~ IL-2 will activate the receptors of T-cells, and accelerate the proliferation of these cells

- Steroids **inhibit the transcription of IL-2**, as a result, it will inhibit recruitment and proliferation of T-cells

- Steroids affect **CELLULAR IMMUNITY** more that humoral immunity.

- **Clinically:**
  1- They are the first line immunosuppressant therapy for both **solid organ and hematopoieticstem cell transplant** (kidney, heart, lung and even bone marrow transplantation) , and for **Graft-versus-host disease**
  [**Graf-versus-host disease**: the T-cells in the bone marrow of the donor attack the host, huge amount of T-cells found in the graft, this occurs in bone marrow transplantation. So we give glucocorticosteroids to reduce the T-cells activity within the body of the host]

  2-Glucocorticosteroids modulate allergic reactions and **useful in treatment of diseases like: asthma, psoriasis الصدفية,** and **atopic dermatitis**. And **whenever the patient has undesirable immune response**

  3- Used to treat **rheumatoid arthritis** and **idiopathic thrombocytopenic purpura (ITP).**

- **Glucocorticoids have many side effects :**
  1- Immunodeficiency
  -The patient will be susceptible to bacterial and viral infections due to long usage of glucocoricosteroids which cause drop in immunity(NO T-cell immunity and reduction of reaction of B-cells)
  - 1/3 of patients after organ transplantation die from infections specially **pneumonia** and **cytomegalovirus (CMV)** [30% of these patients die from CMV]

  2- Adrenal gland suppression

  3-Hyperglycemia

  4-Fat redistribution
  Buffalo hump and moon face as in Cushing disease

  5- Growth failure and delayed puberty
  This is an issue of children, it doesn't affect adults.
  In organ transplantation we have (risk: benefit), maybe the child will have

delayed puberty but in this case,benefit outweighsthe risk.

6- Effects on CNS (euphoria, psychosis)
7- Cataract

8- Osteoporosis

9- Gastric ulcer: with long treatment of glucocorticosteroids either orally or systemic, we used to give with them PPI"Proton Pump Inhibitor" (omeprazole, lansoprazole, esomeprazole) or (misoprostol as prostaglandin E2) to protect the stomach.

- We have in our society **a steroid phobia (cortisone phobia)**, patients refuse to take cortisone especially in the case of children asthma because of cortisone's effect on growth and puberty. They will keep asking and asking again about the effects of cortisone.

- In asthma and allergic rhinitis cases we give **topical (intranasal/ inhaler) glucocorticosteroids**, so they don't go inside the body of the patient so they don't have any of the side effects mentioned above.

- In casewe had to use **systemic glucocorticosteroids**for asthma patients, we give it **at a low dose and for a shot time** (only few 2-3 weeks) then we stop it, so we won't have any side effects.

- These side effects are mostly seen after the steroid treatment of Rheumatoid arthritis and organ transplantation where large doses are used. However, they are NEVER seen with the steroid treatment of asthma whether it was topical or systemic treatment.

- Examples for glucocorticosteroids:
cortisone, prednisone, methyprednisoneand**dexametasone**.

- Dermatologists use creams that contain steroids to treat allergic diseases, for example: psoriasis and atopic dermatitis.

Calcineurine inhibitors: (Cyclosporines , Tacrolimus)

- We combine these drugs with glucocorticosteroids for immunosuppression.

- First, let's talk about **calcineurine** normally:
  calcineurine attaches to **(nuclear factor "NF")** inside the cell, this NF is responsible to go to the DNA and transcribe IL-2.

- So, calcineurine inhibitors, inhibit IL-2 production as in glucorticosteroids but with a different mechanism.
  They bind to calcineurine and reduce their activity toward the activation of IL-2.

- The end result is **decreasing the CEELULAR IMMUNITY**

- They are used similar to corticosteroids :
  1- in **human organ transplantation**
  2- in **Graf-versus-host disease** afterHematopoietic stem transplantation
  3- in selective **autoimmune diseases (psoriasis, rheumatoid arthritis, and SLE)**

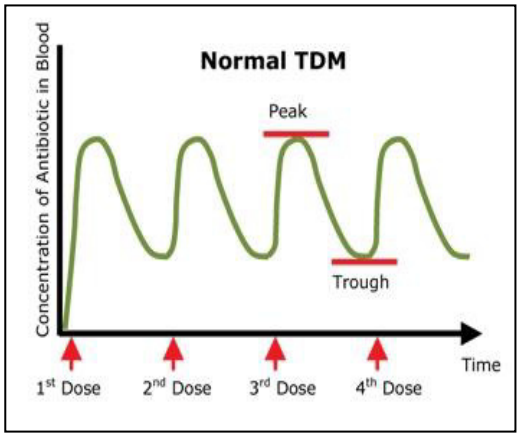
- Their anti-inflammatory activity isquestionary, it is not great, so it is mostly immunosuppressant agent NOT anti-inflammatory.

- They are metabolized by CYP3A4, and we have many agents to activate or deactivate the CYP3A4, so the chance of drug-drug interaction is very high.

- They have very narrow therapeutic index(therapeutic margin/window)

- They have many adverse effects such as:
  1- liver toxicity
  2- nephrotoxicity
  3-hypertension
  4-hyperkakemia
  5-hyperglycemia
  6- viral infection
  7- lymphoma, hirsutism, gum hyperplasia
  8- anaphylaxis after IV administration
  [Don't memorize them all, just you have to know the side effects which will be explained now]

- Most of the **side effects are dose related**, any small increase in the dose will cause toxicity, and any small decrease in the dose will lead to rejection of transplantation. So we are living between very narrow edges. So, **you need to MONITOR your drug.<u>We monitor the cyclosporine's trough levels everytime</u>** to make sure that the level of the drug in the patient's body is within this narrow therapeutic index.
  [If you remember, in second year when we talked about aminoglycosides, gentamyocine specifically,we were afraid of nephrotoxicity,we said that we should monitor tough levels.]

  Trough : is the level of the drug before the next dose

- Also, you should take care of <u>serum electrolytes</u> because calcineurine inhibitors cause hyperkalemia and hypermagnesemia.

- You should monitor the renal function, hepatic function, blood pressure and serum glucose (because these drugs cause

hyperlipidemia).

- These side effects are serious but benefit outweighs risk, because the patient needs that organ!

- The side effects of tacrolimus are the same as cyclosporines EXCEPT it doesn't cause hirsutism and gum hyperplasia, and drug interaction is also the same.

- You should memorize that both calcineurine inhibitors cause:
  1- **nephrotoxicity**
  2- **neurotoxicity (mostly tremor)**
  3- **hypertension**
  4- **hyperglycemia**

- With calcineurine inhibitors :
  ** If you give CYP450enhancer (phenobarbital, phenytoin, rifampin), rejection will happen, because they will enhance the metabolism of your drug.

  ** If you give (erythromycin, clarithromycin, ketoconazole, grape fruit juice) the clearance of the drug will decrease, this will induce toxicity.

- The predominant enzyme responsible for metabolism of tacrolimus and cyclosporine is CYP3A5, but cyclosporine can be metabolized by CYP3A5 and CYP3A4, but tacrolimus is metabolized by CYP3A5 only , so **a genetic variation within CYP3A5 will result in changes to activity of CYP3A5** protein can affect concentration of tacrolimus within the body, in particular, individuals who are homozygous for the G allele (2 alleles have single nucleotidepolymorphism, they become G) , the patientwho has CYP3A5 homozygous mutant on position G, have a non-functioning CYP3A5
  The frequency of the G allele varies worldwide, from

approximately 0.3in some African populations and 0.09-0.1 in Caucasian populations. This mean approximately 9-10% of us have this polymorphism, if they take tacrolimus they can't metabolize it. So these patients should be taken into consideration, and we should monitor trough levels of the drug.

"Individuals homozygous for the G allele have been shown to have higher concentrations of tacrolimus and require lower doses of the drug, as compared to individuals who are not homozygous for the G allele."Wiki

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Sirolimus :

- The last drug in the group of IL-inhibitors
- **Inhibits the CELLULAR IMMUNITY** throw inhibiting kinase activity of mammalian target of rapamycin (**mTOR**)and decrease the IL activity.
  (**mTOR**) doesn't affect the transcription, **it affects the cell cycle**, so inhibiting the cell cycle means inhibiting T-cell proliferation, because the number of T-cells before the activation is not high, but when activation occurs (IL activation) the proliferation will increase.

- It is used **instead of calcineurine inhibitors** (tacrolimus and cyclosporines):
  when the patient can't tolerate the side effects especially if the patient develops nephrotoxicity.
- If the patient can't take glucocorticosteroides, we give him sirolimus instead of it.

- Can cause mental confusion and nephrotoxicity but much less than calcineurine inhibitors.

- Don't forget that the main group of immunosuppressant is glucocorticosteroids, we give it with calcineurine inhibitors or

sirolimus, because we HAVE TO combine drugs.

THE END

- **SUMMARY:**
- Immunosuppressant has narrow therapeutic index
- We use Immunosuppressantin 2 cases:
  - To prevent the rejection in organ transplantation
  - To treat autoimmune diseases
- in organ transplantation rejection will happen, we can't prevent it, we just delay it
- we have 4 types of rejection :
  hyperacute / accelerated / acute / chronic
- we deal with acute and chronic rejection
- immunosuppressant should be given for long time (2-3 years)
- We should combine 2 drugs for immunosuppression to avoid toxicity of a high dose of one drug.
- **Glucecorticosteroids:**
- at low doses work as anti-inflammatory(by increase transcription of lipocortin)
- at high doses work as immunosuppressant(by inhibit transcription of IL-2)
- it binds to GR , then the complex binds to GREin the nucleus , which leads to inhibition of transcription of IL-2
- it inhibits **CELLULAR IMMUNITY**
- we use it :
  - to suppress immunity in organ transplantation
  - to treat autoimmune diseases
  - to treat graft-versus-host disease
  - to treat asthma and allergic reactions [as anti-inflammatory topically]
- it has many side effects:
  immunodeficiency/ growth/adrenal gland suppression /hyperglycemia /fat redistribution/ psychosis / euphoria / cataract / osteoporosis / gastric ulcer
- examples :
  cortisone, prednisone, methyprednisone and dexametasone
- **Calcineurin inhibitors:**
- The main 2 drugs are : **cyclosporine** and **tacrolimus**
- Calcineurin attach to NF inside the cell , go to the DNA, causes transcription of IL-2 , so thecalcineurin inhibitors inhibit this pathway ⟶ inhibit transcription of IL-2
- Inhibit **CELLULAR IMMUNITY**
- similar usage to glucocorticosteroids EXCEPT the anti-inflammatory action
- the side effects :
  nephrotoxicity / neurotoxicity / hypertension / hyperglycemia
- side effects are dose related
- we should trough the level of the drug everytime
- cyclosporines are metabolized by CYP3A4 and CYP3A5 , but tacrolimus is only metabolized by CYP3A5 [so we can have genetic variations]
- Drug-drug interaction can happen:

- Some drugs increase the metabolism of calcineurin inhibitors causing rejection
- Sone drugs decrease the clearance of calcineurin inhibitors causing toxicity

- **Sirolimus :**
- It binds to m-TOR inhibiting the cell cycle NOT the transcription (by inhibiting IL-2)
- Inhibits **CELLULAR IMMUNITY**
- It is used instead of calcineurin inhibitorswhen the patient can't tolerate the side effect , for example : having nephrotoxicity

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Done by : Ola Atif
Good Luck :D