INTRODUCTION TO MEDICAL

IMMUNOLOGY

SLIDE SHEET

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Immunopharmacology

There are many problems in our bodies linked to immunity; like autoimmune diseases and cancer. In autoimmune diseases (such as Psoriasis, Lupus, and Rheumatic arthritis) there is a hyper activation of the immune system towards our bodies. While in cancer, the problem is that the cancer evades the immune system in a way that the immune system can't recognize it. So we need to find a way to deal with these diseases and here appears immunopharmacology (We have to increase the immunity in cancer cases and decrease it in autoimmune diseases).

To really understand the concept of immunopharmacology and how immunotherapy works, we'll start with a kidney transplantation case, where we need to suppress immunity. And alongside we'll mention the treatment for many autoimmune diseases.

In which cases do we need immunotherapy?

1- In preventing the rejection of organ or tissue grafts. And this is very important to understand; since the cases of BM and kidney transplantation are very high here in Jordan. And cases of kidney failure are increasing more and more.
2- Treatment of certain diseases that arise from dysregulation of the immune response such as autoimmune diseases (lupus, psoriasis, arthritis, ulcerative colitis, and many more) and immunodeficiency cases like AIDS.

Let's start with kidney transplantation. Always remember that when we transplant an object there is a chance for rejection and this rejection could follow one of these patterns (hyper-acute, accelerated, acute, and chronic).

** Actually we can't do anything to the hyper-acute and accelerated rejections, they happen once we transplant a kidney or anything and they are much related to each other.
** In immunopharmacology we only deal with acute or chronic rejections (acute means within a month, and chronic means after 1 month or 3 months depending on the guidelines).

QUESTION: Why do these rejections happen?

As transplantation introduces a foreign material to the body, this is going to produce antigens that will be recognized by the immune system. The immune system now sees this foreign body as a bad object and starts producing lymphokines (including IL-2) and further activation for the immune system happens which leads to a nasty cycle of foreign tissue destruction and rejection.

So when you do a heart, lung, kidney, or cornea transplantation (in other words any graft including the BM), you introduce foreign antigens to your patient and at the end rejection will happen. *They are antigenic.* And the only solution to prevent rejection is that we have to suppress the immunity of the patient; and since the patient cannot live without immunity we always have to balance between the need for the immunity and the need to suppress it to prevent rejection. It's not an easy thing at all, it's very complex!

Immunosuppressive drugs are used in these cases, they are very challenging with so many complexities but there is no other option; the patient will either die from kidney failure or will undergo kidney transplantation and take these drugs. We never transplant for a joke!

QUESTION: What are the problems associated with these drugs?

1- Very narrow therapeutic index so the dose given should be very limited.
2- Treatment is very complex and actually we cannot build our regimen on one single agent, we usually combine many of them together to make sure no rejection takes place. The reason behind using a combination and not a single drug is that these agents are very toxic and there is no single agent that can be tolerated by the patient. Also, we need different mechanisms to inhibit the immune system because one inhibited step might not be enough for immune suppression!
3- Low patient compliance: patients don’t take drugs seriously.
4- Pharmacokinetic interactions are high and can cause serious diseases.
5- These drugs can increase the risk of many diseases, like infections and malignancies! It would be so hard convincing a patient to take a drug that might lead him to cancer, but you should do it!

**Mothers sometimes skip doses for their ALL child to make him/her suffer less, but actually they're making his/her situation worse! So drugs should be taken seriously with no emotions.*

DRUGS USED IN IMMUNE SUPPRESSION

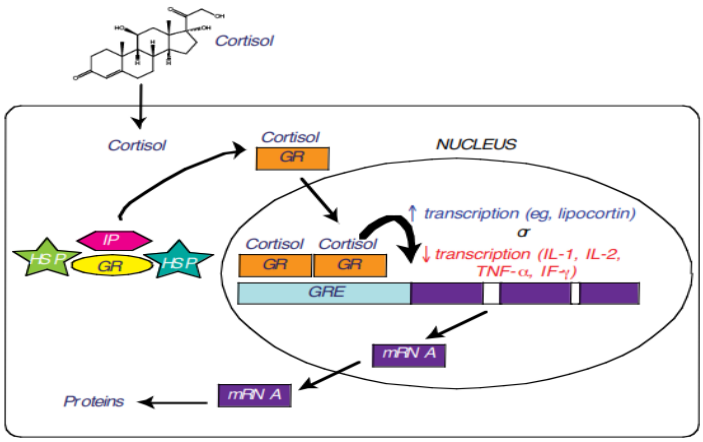
Here is a brief description about each family and they will be discussed in details in these 2 lectures.

1- **Glucocorticoids (steroids)**
   We took them as anti-inflammatory drugs in many cases but here we'll look at a different side of their action which is immune suppression in organ transplantation. They're magical drugs and have different outcomes wherever you throw them; they have a great value but also huge side effects!
   They are used in Asthma, allergic rhinitis, psoriasis, ulcerative colitis, and cancer.
2- **Calcineurin Inhibitors:** cyclosporine A and Tacrolimus.
   They affect the production of IL-2 since cell-meditaed immunity depends mainly on IL-2.
3- **IL-2 Receptor (mabs):** Basiliximab and Daclizumab.
   They inhibit the receptor of IL-2
4- **Anti-metabolites:** Azathioprine, Mycophenolate, and Leflunomide.
   They inhibit the cellular immunity by inhibiting the production of immune cells; they act as false nucleosides to terminate the replication.
5- **m-TOR inhibitors**: Sirolimus.
   m-TOR (mammalian target of rapamycin*) is a kinase responsible for a checkpoint between G1 and S. so these drugs inhibit the replication.

*Rapamycin is just another name for Sirolimus.

1- Glucocorticoids

They are widely seen everywhere. They are called the magical drugs and have two main effects; anti-inflammatory and immunosuppression.



Cortisol binds to corticosteroid receptor in the cytoplasm, and then this complex enters the nucleus and binds to its specific binding site. There it increases the transcription of lipocortin *(related to its anti-inflammatory effect)* and inhibits the transcription of IL-1, IL-2, TNF-alpha, and IFN-gamma *(related to the immunosuppression effect).* IL-2 is very important and causes self-stimulation of the T-cells. Glucocorticoids also suppress the humoral immunity causing B cells to express smaller amounts of IL-2 and IL-2 receptors. <u>But keep in mind that cellular immunity is affected more than humoral immunity.</u>

And this can be achieved depending on the dose:

- At **low doses**, cortisol increases lipocortin which results in **anti-inflammatory** effect.
  For example, Asthma patients are given 20 mg twice daily. This dose is enough as an anti-inflammatory (by increasing lipocortin) but can't induce immune suppression.
- At **high doses**, cortisol decreases the above cytokines which results in **immunosuppression** effect.
  When we give 60 or 80 mg we'll have both effects (the anti-inflammatory and the immune suppression)

When do we use Glucocorticoids?

- It’s the first line therapy whenever we think there is an immune response; because they work fast!

- It's also the first line immune suppressive therapy for both solid organ and hematopoietic stem cell transplantation. Therefore, 6-24 hours before the transplantation, we give the recipient injection of 500 mg steroid which is very huge and enough to suppress all the T-cells to prevent any possible rejection because rejection is easier at the beginning.

- In Idiopathic Thrombocytopenic purpura (ITP) which is a decrease in platelets with no known reason and in Rheumatic arthritis.

- If there is a need to decrease T-cells and prevent their activation.

- As **premedication** for other agents that might cause undesirable immune response, an example for that is the pigment or the contrast media given before kidney or blood vessels imaging. 1-2% of people are allergic to it, so cortisol is given 2 days before the injection of this media as an immunosuppressant (this is an **acute** use of cortisol).

- **Asthma**: It's an allergy with inflammation, so **there are no drugs like corticosteroids in reducing allergic asthma!** They’re used at low doses as inhalers because of their toxicity (**Chronic** use).
  Oral prednisone could also be given for 7 days to reduce the flare of the asthma, It's safe and doesn't cause serious side effects "will be mentioned in a moment" but it causes hyperglycemia and hypertension "they are reversible in the beginning when you stop the drug"
  **Note: most of the inhalers are corticosteroids because they are very effective.*

Always remember to start with glucocorticoids because they work fast!

*Remember that Rheumatic arthritis is treated with Disease Modifying Anti-rheumatic drugs (DMARDs) including leflunomide, methotrexate, and azathioprine. These drugs need six weeks to cause their effect! And this is too long and we can't wait, so we give the patient glucocorticoids at the beginning. This is called bridging therapy.

*Another example for bridging therapy is warfarin with low-molecular weight heparin.

THE SIDE EFFECTS OF GLUCOCORTICOIDS:

1- Immunodeficiency
2- Adrenal gland suppression
3- Hyperglycemia (insulin resistance) and fat redistribution (buffalo hump and moon face)
4- Growth failure and delayed puberty
5- Psychosis, personality changes and depression "this is serious!"
6- Osteoporosis
7- Cataracts
8- Gastric ulcers

☞ These side effects are dose-dependent so they will appear more in transplantation.
For a kidney recipient for example, we give him 500 mg before the transplantation and in the following 6 months we'll give him glucocorticoids at a lower dose combined with other agents. And in the other following 6 months we'll taper the dose because he has undergone adrenal gland suppression.

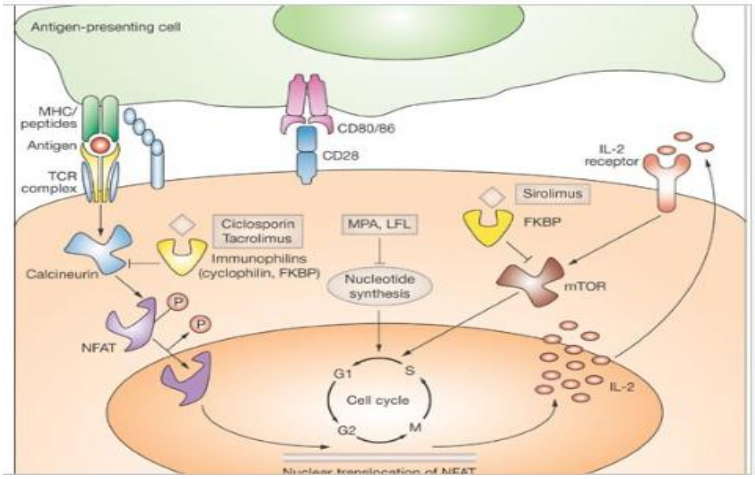
☞ If the patient stops taking cortisol, some of these side effects will disappear (they are reversible) but others won't. The irreversible ones are **diabetes** and **osteoporosis**.

☞ Inhalers (used in Asthma in normal doses twice a day) have no side effects except thrush in the mouth as a result of the immunosuppression in the mouth and the following candidiasis.

- ☞ Cortisol is not a curative treatment; it only decreases the symptoms and morbidity (Not mortality).

- ☞ They have so many serious side effects but the benefits outweigh the risks and you need to convince your patient to overcome the cortisol phobia and take them.

2- Calcineurin Inhibitors



Antigen presenting cell binds to the T-cell receptor through its MHC molecule forming (TCR-MHC complex) and also binds to the co-stimulatory signal forming another complex (CD28-CD80 or 86). The end result of these two signals and binding is the autocrine activation of the T-cell which is facilitated by the activation of Calcineurin (*Calcineurin is a protein that's activated through Calcium*).

The activated Calcineurin will bind to the **nuclear factor of activated T-cells (NFAT)** and then will enter the nucleus. There, it will stimulate the production of IL-2 which in turn activates the interleukin receptors on the same cell and nearby cells; this is called autocrine effect and parcrine effect, respectively.

And because the rejection is caused by T cells in the first place "cellular immunity", we can use drugs here to stop the T-cells activation, thus preventing the rejection. Unlike glucocorticoids that are non selective in their suppression of the immunity, Calcineurin inhibitors are more selective to the real cause of rejection which is T-cells.

So in the beginning before transplantation we give 500 mg glucocorticoids. And after transplantation we reduce the dose to 60 or 80 mg and add other drugs (like Calcineurin inhibitors) to make sure that T-cells are not replicating and causing rejection.

Examples for Calcineurin inhibitors are **Cyclosporine** and **Tacrolimus**. Each one of them binds to a specific inhibitor in the cell (immunophillins); Cyclosporine binds Cyclophilin and Tacrolimus binds FKBP. Immunophillins then bind to Calcineurin and inhibit it. The net result will be inhibiting the production of IL-2; so there will be no autocrine and paracrine activation for T cells (We reduce the risk of rejection).

** These two drugs are very similar but Tacrolimus is better *(we'll talk about this point).*

When do we use Cyclosporine and Tacrolimus? (And few notes about these uses)

1- In human organ transplantation (liver, cornea, kidney, heart, or any other graft)
2- In GVHD after hematopoietic stem cell transplantation (This graft might have T-cells from the donor so we have to inhibit their function).
3- In selected immune disorders like psoriasis, rheumatic arthritis, and even asthma. But uses here are very limited. **And these drugs are mainly used as immunosuppressants.**
4- In severe dry eye syndrome and ocular graft-versus-host disease. It's available as cyclosporine ophthalmic solution. (If we transplant a cornea or a valve "Ahmed's valve in closed angle glaucoma" and rejection happens, we give cyclosporine).
5- Cyclosporine can be used alone or in combination with other immunosuppressants such as corticosteroids especially in kidney transplant.
6- In combination with methotrexate, cyclosporine is a standard prophylactic regimen to prevent GVHD after allogenic stem cell transplantation.

These drugs are complex and also not a joke! Their complexity comes from the fact that:

- They have very narrow therapeutic indices that's why monitoring is a must!
  And side effects could be from high or low doses; as high doses cause toxicities (nephrotoxicity*[1], mental confusion, hyperglycemia, and hypertension) and transplant rejection will happen at low doses.

  [1]You are giving a drug that might lead to nephrotoxicity to a kidney transplant patient! But you have no other options!
  **These drugs only succeed in 50% of graft cases only.*

- The levels of these drugs vary a lot in our bodies; this is because they are metabolized by CYP3A4 which is affected by so many things in our lives. And even the levels and functionality of CYP3A4 are highly variable from person to another which leads to mare variability in the levels of Cyclosporine and Tacrolimus.
- They increase the incidence of lymphoma and other cancers (Kaposi sarcoma and skin cancer).

Antibiotics like Azithromycin, Clarithromycin, and Erythromycin inhibit CYP3A4 affecting by this cyclosporine and warfarin levels. So NEVER give a transplant patient with bacterial infection these drugs! They will inhibit CYP3A4 and the levels of cyclosporine and its toxicity will increase! (They have very narrow therapeutic windows).

Monitoring parameters for Cyclosporine

1- **Cyclosporine trough levels**
   cyclosporine is given at the end of transplantation, and we measure its dose before giving the 2nd drug (we measure the trough). We keep measuring the trough day by day "at the beginning" then week by week to monitor its level and see if there is a need to increase or decrease the dose. There is no joke here and the worst toxicities are nephrotoxicity and kidney rejection.
   **Gentamicin is also monitored in the same way*.

2- Serum electrolytes "some of them cause hyperkalemia"
3- Renal function
4- Hepatic function
5- Blood pressure
6- Serum cholesterol "cyclosporine increases the level of cholesterol"

Cyclosporine is the same as Tacrolimus; they are both Calcineurin inhibitors and have the same high toxicity but we say Tacrolimus is better as it does not cause hypercholesterolemia like cyclosporine and is more efficacious than it. Besides that, Tacrolimus could be combined easier with glucocorticoids. But both can be used as they are comparable to each other.

*Please excuse any typographical and grammatical errors!

GOODLUCK