Immunology – pharmacology

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This sheet topics:

- ☑ Immune suppressants
- ☑ Some Autoimmune-diseases drugs
- ☑ Cancer immunotherapy

Immune suppressants

➲ We give immune suppressants mainly when we want to transplant organs.

Why?

[1]-To suppress the antigenic rxn that occurs upon transplantation which damage the transplanted organ.

→The severity of this immune rxn is determined by who is the donor and how much the dose >> does the transplanted organ match the patients antigens (rem. MHC-match test).

→The immune rxn here is driven by T-cells –mainly-, so we want to decrease T-cell immunity.

[2]- We use immune suppressants to decrease the chance of rejection (which is very high even with these drugs >> 40-50% of kidney transplantations fail).

[3]-To overcome the immunity defense lines we must use many approaches and mechanisms.

Types of rejections:

1. Chronic.
2. Acute.
3. Subacute, here the rejection happen right when u transplant the organ as the immune system attack it.
   (we mainly are going to deal with acute and chronic).

Notes:

- ✓ Immune suppressants are given to the patient before and after transplantation.

✓ Bone marrow transplantation is a special case as it's not enough to give only the recipient immune-suppressants but also the donor>> as its BM is full with his immune cells.

❖ Agents that modulate the immune system play an important role in:
1. Preventing the rejection of organ or tissue grafts.
2. In the treatment of certain diseases that arise from dysregulation of the immune response.

- Autoimmune diseases (like rheumatoid arthritis\ IBDs).
- Immunodeficiency diseases.
- Cancer.

- Four types of rejection can occur in a solid organ transplant recipient: **hyper-acute, accelerated, acute,** and **chronic.**

⦿ 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

Transplant Rejection agents complexity

- Many problems exist in currently approved regimens:

1. **Treatments are often very complex.**
2. **low patient compliance.**
3. **Therapeutic margins can be very narrow.**
4. **Pharmacokinetic interaction potential is high and causes problems.**

➲ Complications of immune-suppression:

1. Infections.
2. Cancers [ex. Cyclosporine, an immune suppressant, causes lymphoma, skin cancer & Kaposi sarcoma].

==========

These are the groups of drugs that are used in immune suppression→

Groups

- **Glucocorticoids**
- **Calcineurin inhibitors**
  - **Ciclosporin A**
  - **Tacrolimus**
- **IL-2 receptor 'mabs'**
  - **Basiliximab**
  - **Daclizumab**
- **Anti-metabolites**
  - **Azathioprine**
  - **Mycophenolates**
  - **Leflunomide**
- **m-TOR inhibitors**
  - **Sirolimus**

- A quick note:
  Anti metabolites are also used in cancer these drugs are aggressive >> here we use them in a low dose as immunosuppressant.

→Example:
In Psoriasis الصدفية (an autoimmune disease) we give the patient only 7 mg of methotrexate , an antimetabolite, twice weekly.
In CML we give it IV in a really high dose.
Explanation: cancerous cells are mutated in a drug-resistant way → hard to kill → the dose must be really high.
While when we want to suppress immunity → we want to kill normal lymphocytes → easy to kill → the dose is low.
Strategy of Anti metabolites → they deplete the cell from metabolites → stop its proliferation.

Now let's discuss these groups of drugs in details ☺.

First: Corticosteroids

- Glucocorticoids suppress the cell-mediated immunity more than humoral immunity.
- Inhibiting genes that code for the cytokines, the most important of which is **IL-2.**
- 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.
- **MOA**: corticosteroids are very lipophilic >> work intracellularly and alter things at gene level.
  What exactly happen: look at fig1 and read its key.

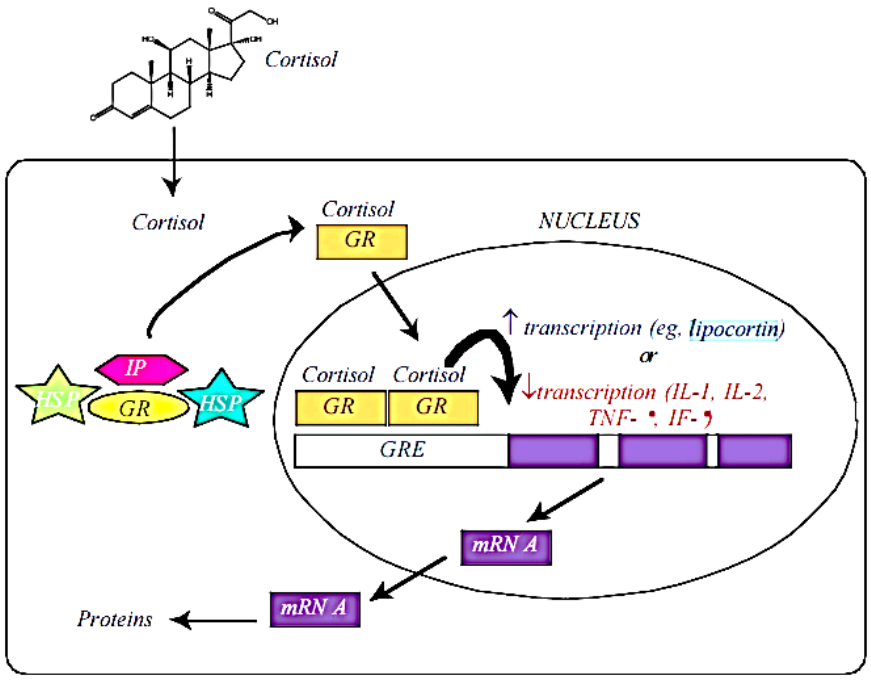

Figure 1:MOA corticosteroids, *gluco-corticosteroids bind their gluco-corticosteroid receptor at the cytoplasm.>> this complex enter the nucleus >> bind DNA and inhibit the transcription of cellular immunity mediators (IL-1 , IL-2, TNF-alpha & IF-gamma) & increase the transcription of lipocortin , which have an anti-inflammatory activity.*

Corticosteroids the magical drugs

Corticosteroids are popular for their anti-inflammatory effect because they increase Lipocortin expression, to the extent that we call other anti-inflammatories as non- steroidal anti-inflammatory (NSAID), also they reduce the hypersensitivity very well because they inhibit the expression of IL-1\IL-2\TNF-alpha\IF-gamma.
We have another magical drug in pharm. Which is morphine >> morphine is said to be magical, too.

☒ Side effects of corticosteroids الحلو ما بيكمل

Corticosteroids have many side effects >> simply, because they interfere with gene excerption.

These are:

1. Immunodeficiency.
2. Adrenal glands suppression.
3. Hyperglycemia.
4. Change Fat redistribution >> buffalo hump and moon face.
5. Growth failure, delayed puberty.
6. Excitatory effect on central nervous system (euphoria, psychosis).
7. Osteoporosis.
8. Cataracts.
9. Gastric ulcers (prevent with omeprazole, misoprostol).

Notes:

- ✓ These side effects manifest only with **chronic** (prolong) **systemic** use, this implies the followings:
- ✓ In asthma and allergic rhinitis → corticosteroids are the drug of choice and we do not expect them to cause a lot of side effects as they are not prescribed as intranasal or oral inhalers not systemically. But in Psoriasis or SLE (lupus) → they are prescribed systemically (orally) → a lot of side effects are expected.
- ✓ When treating a child with exasperated asthma → we must give him corticosteroids to reduce his hypersensitivity→ we start them orally for 5 days to one week, then we change it into an inhaler.
  Do we expect such a child to produce side effects like growth failure, delayed puberty?
  No, because the oral systemic administration is for a short time.
- ✓ When prescribed for a short time → they will not produce side effects.
- ✓ Tapering of corticosteroids is required when prescribed for a long time → because the adrenal gland is suppressed and need time to re-function.
- ✓ Tapering of corticosteroids is not required when prescribed for short time (like, one week); corticosteroids need at least one month of continuous use to suppress the adrenal gland.

Second: Calcineurin Inhibitors

- ✓ **Calcineurin** is a cytoplasmic phosphatase**,** a downstream protein of the activation cascade of T-cell.
- ✓ Two drugs under this category Cyclosporine & Tacrolimus.

Figure2 shows the MOA of three groups (Calcineurin Inhibitors, mTOR inhibitors & IL-2 receptor inhibitors).

Very important figure

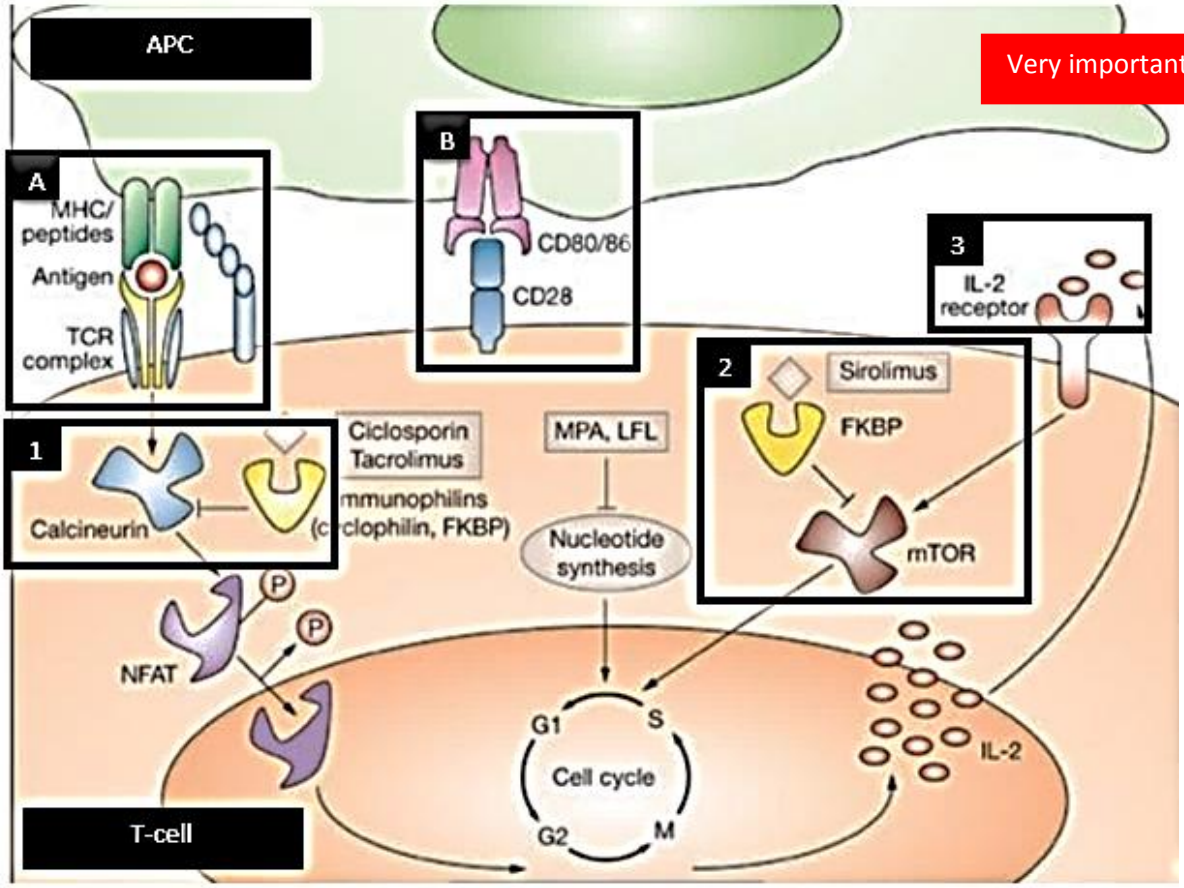

Figure 2: T cell activation and MOA of some immunosuppressant drugs.*to activate T cell we need two signals the presented antigen on MHC molecule by APC (indicated as "A')and the co-stimulatory signal mediated by CD28 /CD40 "B"*

1:calcineurin participate in the activation cascade ,once it is phosphorylated, it enter the nucleus and initiate IL transcription, calcineurin inhibitors inhibit it and subsequently suppress T cell activation and proliferation.

*2:activated T cell secrete IL-2 , IL-2 aids in auto-proliferation of T cell >> can be inhibited by IL-2 receptor blockers (**Basil**iximab) باسل.*

3: mTOR goes to the cell cycle and makes it goes really fast of T-cell >> mTOR can be inhibited by sirolimus.

➲ So immune suppression is all about finding a drug-able target.

Now back to Calcineurin Inhibitors

→Cyclosporine & Tacrolimus have similar MOA with minimal differences:

Tacrolimus is more expensive but with milder side effects (unlike cyclosporine it does not produce gingival hyperplasia & hairism زيادة نمو الشعر) .

**Remember from CVS , calcium channel blockers also cause gingival hyperplasia.

✓ <u>Therapeutic uses:</u>

1. human organ transplantation,
2. graft-versus-host disease after hematopoietic stem cell transplantation,
3. selected autoimmune disorders.

Graft versus host disease (GvHD) is a condition that might occur after an allogeneic transplant. In GvHD, the donated bone marrow or peripheral blood stem cells view the recipient's body as foreign, and the donated cells/bone marrow attack the body. Marrow or peripheral **blood stem cells** view the recipient's body as foreign, and the donated cells/bone marrow attack the body.

<u>Complications and complexity of administration:</u>

Complexity

- metabolized by the P450 3A enzyme system in the liver with resultant multiple drug interactions.
- Narrow therapeutic window
  - Levels too high: toxicities (i.e. nephrotoxicity, 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,

Erythromycin is CYP3A4 inhibitor>> it is contraindicated with cyclosporine.

Because of these complication we always monitor these drugs >> by knowing the TROUGH

- The **trough** level is the lowest concentration in the patient's bloodstream, therefore, the specimen should be collected just prior to administration of the **drug**. The peak level is the highest concentration of a **drug** in the patient's bloodstream. Figure3
  →The drug should always be within the therapeutic index, away from the peak in order not to cause nephrotoxicity, and away from the trough in order not to cause transplant rejection.

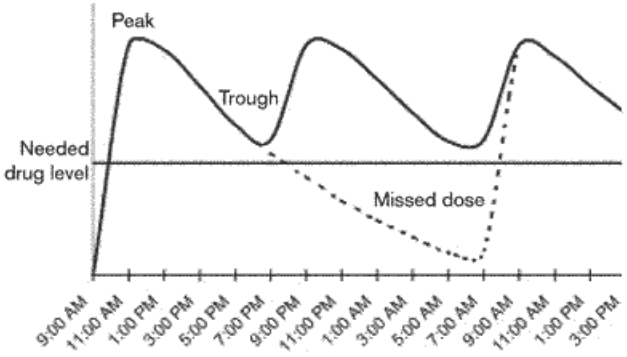

Figure 3: Trough and peaks.

Monitoring Parameters:

- Cyclosporine trough levels.
- Serum electrolytes.
- Renal function.
- Hepatic function.
- Blood pressure.
- serum cholesterol.

Another application for cyclosporine →ophthalmic use→Cyclosporine ophthalmic solution is now available for severe dry eye syndrome, as well as ocular graft versus-host disease.زراعة القرنية

Third: Sirolimus

MOA:

1. Inhibit mTOR.
2. Decrease IL-2 level.

- ✓ narrow therapeutic index drug
- ✓ a lot of side effects >> as it interfere with genes
  - Levels too high: toxicities (i.e. mental confusion, nephrotoxicity)
  - Levels too low: transplant rejection
- ✓ monitor by observing → the trough

Note::: we consider sirolimus and Calcineurin Inhibitors as one strategy while corticosteroids and anti-metabolites each is distinct group.

Fourth: Anti-metabolites

- In immunotherapy, they are used in smaller doses than in the treatment of malignant diseases.
- They affect the proliferation of both T cells and B cells.

Regimens

We are concerned with 1 antimetabolites : Azathio**prine** which :

- ✓ Inhibit **purine**s synthesis.
- ✓ Inhibit both B and T cells (non-selective).
- ❖ By now we can make a regimen of immunosuppressants to prevent ACUTE rejection in organ transplantation we give the patient Cyclosporine **OR** Tacrolimus **AND** Azathioprine.

AND at the beginning of the treatment we also give the patient gluco-corticosteroids.

<u>Knowing that Cyclosporine **/**Tacrolimus are enough to suppress the antigenic rxn, why we add azathioprine ?</u>

- Cyclosporine **/**Tacrolimus are very effective drugs yet, if we want to use them alone we must use a VERY high dose → knowing that all these drugs are of narrow therapeutic index → we cannot increase the dose → we add another drug with different MOA instead.
  NOTE : we can apply this to the other drugs , too.

Summary: Cyclosporine\Tacrolimus+Azothioprine+Glucocorticosteroid.

- For **high-risk-rejection patients** (إللي بكون حاسس إنه الزرع حيفشل إلهم لإنو غالباً بكون العضو مسروق و أبصر من وين جاي)

✓ We use Cyclosporine **OR** Tacrolimus AND **Mycophenolate** AND glucocorticoids.
MYCOPHENOLATE : this drug is expensive but effective better than Azathioprine.

Summary for high - risk patient:Cyclosporine\Tacrolimus +Mycophenolate + Glucocorticoids

Remember we always keep monitoring the patient. If we transplant a kidney → we keep monitor its function (by checking the creatinine level..etc)
what if we observe **REJECTION** after the transplantation and after dosing the patient with my immune suppressants regimen ?
-well, is there any drug we forget to use, HA?

We use the fifth group of immune suppressants: **anti-IL-2**.

Fifth: IL-2-receptor antagonists

[1]-Basiliximab.

[2]-Daclizumab.

Read this slide and last 4 lines are very important.

IL-2-receptor antagonists

Ab specific for the high-affinity IL-2 receptor is expressed only on activated T-cell, blocks proliferation of T-cells activated in response to the alloantigens of the graft.

Basiliximab is said to be "chimerized" because it consists of 25 percent murine and 75 percent human protein.

Daclizumab is 90 percent human protein, and is designated "humanized."

Both agents have been approved for prophylaxis of acute rejection in renal transplantation in combination with *cyclosporine/t*acrolimus and corticosteroids.

To treat donor's bone marrow before it is transplanted.

Notes:

- ✓ These are T-cell selective.
- ✓ Declizumab is much expensive than Basil as it is humanized.

➲ Why don't we use these from the very beginning?
Why we preserve these for rejection only?
-because these will block IL-2 receptor ultimately → not just inhibit its transcription like the rest of the drugs → this implies that these drugs will have A LOT of side effects. (no IL-2 at all).

***The Dr focus on the fact that we give BM donor BASILiximab.

❖ DOSING

Don't memories the doses just know when we give each drug before or after transplantation.

☒ For Kidney transplantation:
1- we give Methyl Prednisolone (corticosteroid) 500 mg IV just prior to transplantation and again after 24 hours of transplantation . – this dose is really high (corticosteroids >>before and after)

2- Tacrolimus led **triple therapy**:
-after the transplantation

- **Tacrolimus** 0.1 mg/kg/day given as two doses at 10:00 and 22:00
- **Prednisolone** 20 mg once daily at 08:00
- **Azathioprine** 1-2 mg/kg (usually 75-100 mg) at 08:00 and

Initially 1-2 mg/kg once daily. Maintenance 1 mg/kg once daily.

Notice : here we are giving corticosteroids for a really long time (6 months) and with initial high dose → after 6 months it's the time to stop the treatment but we cannot terminate corticosteroids suddenly (as we are concerned with adrenal suppression) → we need to do tapering.

Prednisolone

Normally reduced according to the following schedule:

- **20 mg daily 1 month started on day 2**
- **15 mg daily 1 month**
- **10 mg daily 1 month**
- **5 mg daily thereafter**

This schedule may be altered if rejection occurs.

- **All patients to receive Ranitidine (150 mgs od) along with Prednisolone.**
- **Steroid withdrawal should be discussed with the patient and they should be informed of the risk of rejection.**
- **The steroids should be withdrawn according to the following schedule:**

Decrease by 1 mg per month till 0mg

❖ Autoimmune diseases.

The key of autoimmune diseases treatment is to know their mediators.
we are going to take two example :

➲Rheumatoid arthritis:

Of two types:

- ✓ RA with T cell involvement in autoimmunity (80%).
- ✓ RA with B cell involvement in autoimmunity (20%).

When treating RA we give first anti-T cells drugs → if no response → we give Anti-B cells drugs.

In RA with T-cell involvement the main mediator is TNF-alpha.
So simply we give the patient **anti-TNF drugs**.
What are these ?

Infliximab and Adalimumab

Collectively when treating RA patient , we give the patient :

1. Corticosteroids for 2 months.
2. NSAIDs to reduce pain.
3. DMARDs (Disease-modifying antirheumatic drugs) , DMARDs include:
    - **Methotrexate** , given for lifelong, needs 2 months for activation (as we give the patient a really low dose 7.5.-15 mg weekly). During these two months we give the patient bridging therapy which is gluco-corticosteroids mentioned above, after these two months we terminate gluco-corticosteroids therapy and proceed with methotrexate.
      →Methotrexate reduce autoimmunity.

4. Anti-TNF (Infliximab and Adalimumab) ,
    - These are given if the patient did not improved by methotrexate.
    - MOA: by inhibiting TNF-alpha this will expression and the activity of (IL-6,IL-1, IL-8) >> this will decrease osteoclast activity >> reduce bone and cartilage erosion.

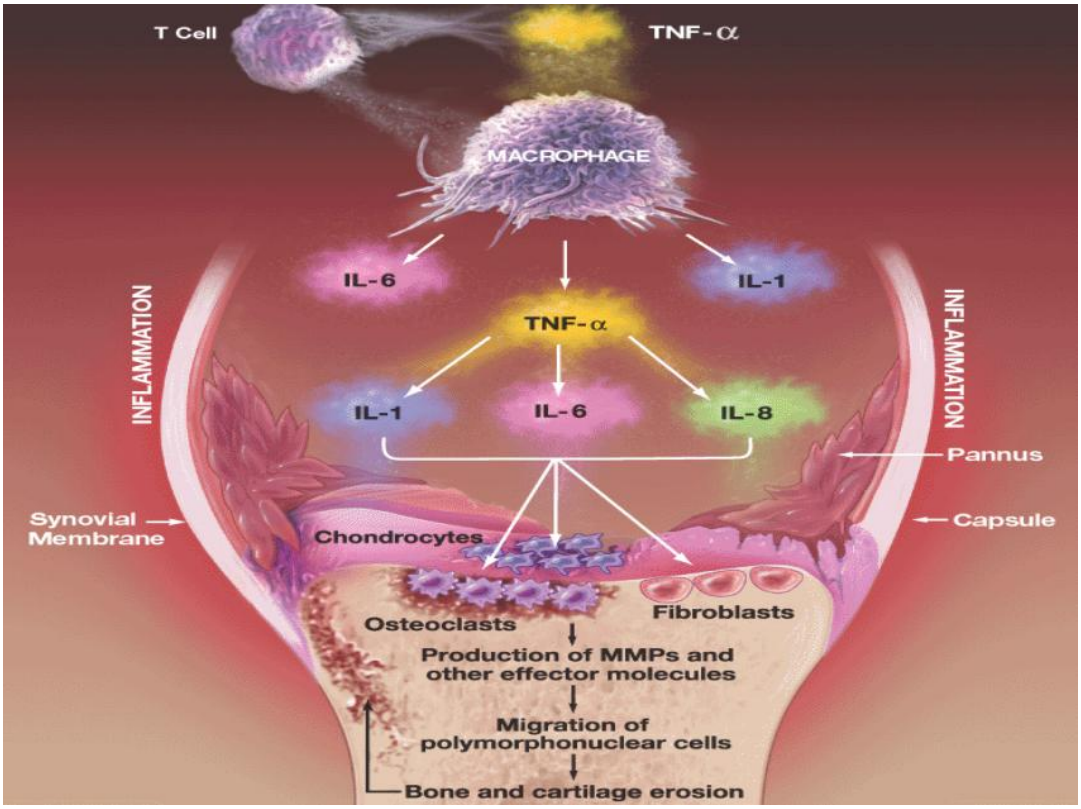

Figure 4: MOA of anti-TNF drugs

Side Effects of TNF Inhibition

- **Infection**
  - Tuberculosis
  - Serious resulting in death
- Neurologic
  - Multiple Sclerosis, seizures, inflammation of the ocular nerve
- Worsening of Congestive Heart Failure

- Remember

STOP if develop a fever, have an infection,

5. Anti-B cell drug (if all previous drugs fail) which is Rituximab.

- We have talk about it in B-cell lymphoma in HLS.
- Anti-B cell (CD20) antibody**.**
- Given in combination with methotrexate.
- Indicates the rheumatoid arthritis has a B cell component to its pathology

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➲Atopic asthma

→The patient has elevated serum IgE.
→We give patients anti-IgE drugs:
Omalizumab (Xolair©) >> expensive 8000$ >> given only if the patient's asthma has exasperated.
→Biologic antibody therapy (Omalizumab; Xolair) binds IgE in the circulation and prevents it from activating mast cells and basophils.
→ Anti IgE therapy is recommended as an add-on to optimized standard therapy in asthmatics 12 years and older who need continuous or frequent treatment with oral corticosteroids.

❖ Immune-stimulants

In all previous states, we wanted to suppress immunity,
actually in pharmacology we always want to suppress immunity, unless in these two cases:

- Cancer
- Viral infection

Invaders of these two conditions always try to escape immune system and they always take advantage of normal regulatory anti-immune mediators.

❖ Cancer Immunotherapy

• Immune checkpoints refer to inhibitory pathways of the immune system that are crucial for maintaining self-tolerance and modulating the duration and

amplitude of physiological immune responses in peripheral tissues in order to minimize collateral tissue damage.

• Tumors misuse immune-checkpoint to evade the immune system clearance, in particular to avoid tumor-antigen specific T-cell responses.

☒ We will focus on Anti PD-1 , anti-CTLA4.
Cancer cells do not just escape the immunity; they also try to kill the immune cells, by inducing its apoptosis by PD + PD-L interaction (programmed death).
OR try to reduce its activity by enhance the action of CTLA-4.
So we give the patient Anti PD-1 , anti-CTLA4 mabs.

Look at Figure5

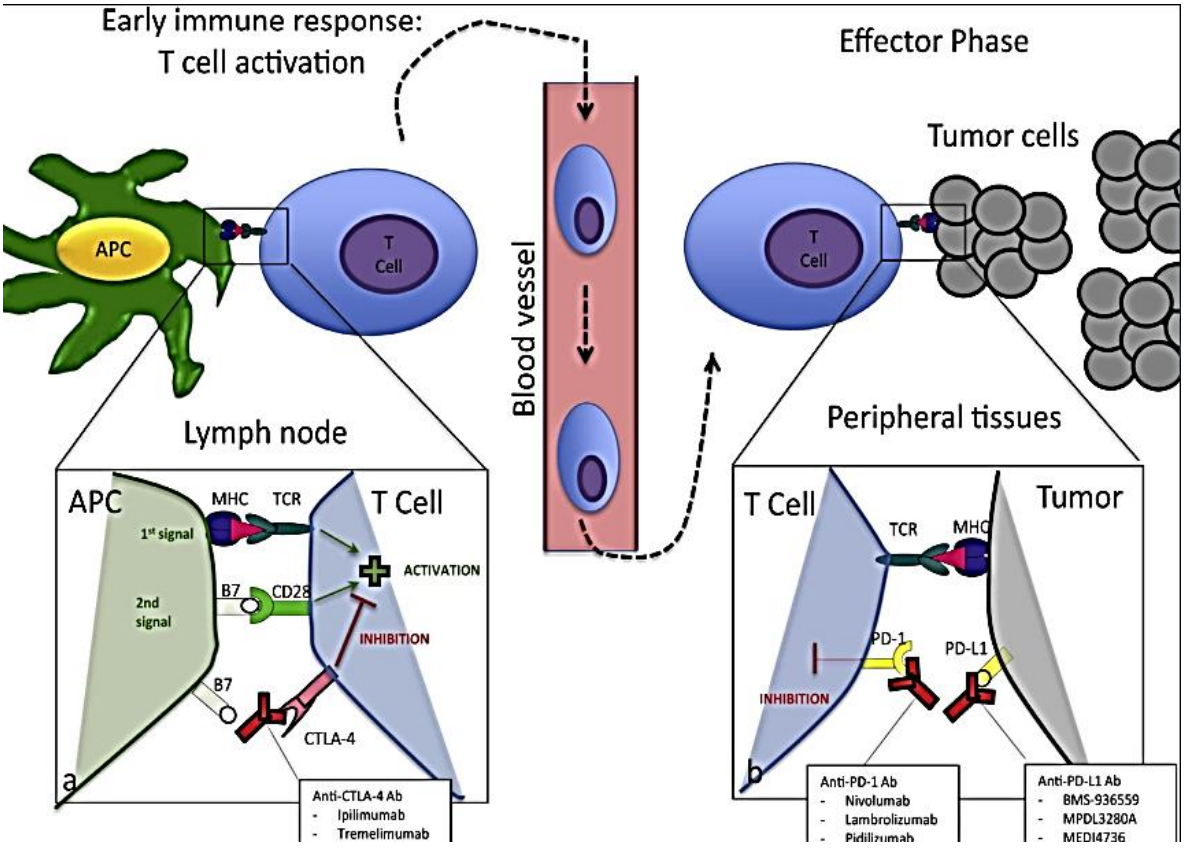
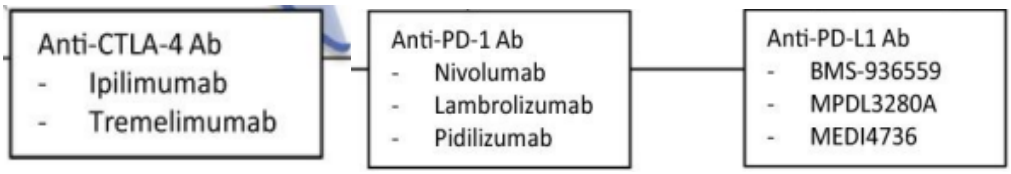


Figure 5 Anti-CTLA4 , Anti-PD1, Anti PDL1.



Anti PD-L 1 are not approved yet (have no names just a code).

Memorize the 1st drug of the other two categories.

These drugs are very effective (in 20% of patients) but are very expensive.

Why only 20% of patients?

-because not all cancers have immunity involvement.

The rest of the lecture is not included in the exam material (last 3 minutes ☺).

وسلامة خيركم ..