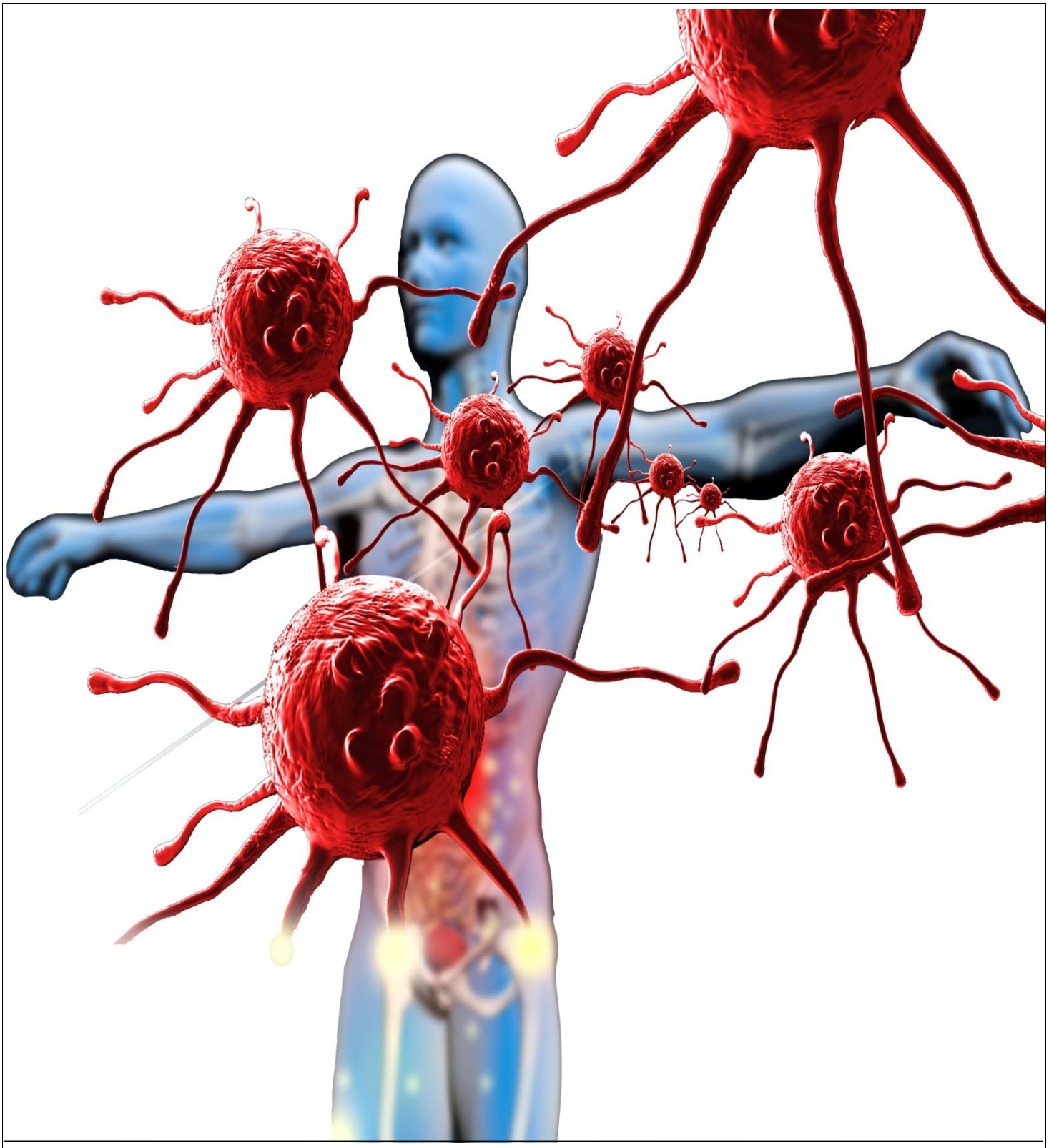

IMMUNOLOGY

Done By: Aseel Olaimat

#23

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Immunopharmacology :

Salaam every one ^^

بسم الله

We were talking about Immunosuppressant mechanisms, and will continue with the Anti-metabolites Drugs (which are one of the Immunosuppressant mechanisms in which the drug binds to either purine or pyrimadine to inhibit cellular and humoral immunity), and talked about 1st drug which was: Methotrexate.

Now, the 2nd Drug is:

Azathioprine

The main drug in this mech., although we said micophenolate is better tolerated and has better activity, but the regimen (بمعنى الوصفة) which the Drs. used to use is the combined regimen which have (Glucocorticoid + Cyclosporine/tacrolimus + Azathioprine).

We leave micophenelate (which is highly Anti-metabolite) to the pt. who has a high risk for rejection and pt. Who can't tolerate Azathioprine.

Now listen, Suppose you have a kidney transplantation surgery, what do you have to do ?

1. We give the patient high doses of corticosteroids:

- MethylPrednisolone(500mg, IV) must be given 1-2hs prior the transplantation.

Written by Aseel Olaimat

- MethylPrednisolone(500mg, IV) must be given after 24hs .

2. Now, then we give the pt either:

- cyclosporine led therapy.
- or tacrolimus led triple therapy (tacrolimus + prednisolone + Azathioprin) ➔ given in 1st 6 months in high doses and we have to monitor the conc., in the 2nd 6 months we cut half the dose for all three drugs.

And keep in your mind that the timing for giving the dose is very important in organ transplantation.

- ok? suppose now your pt will reject the graft !

- listen, in rejection cases, in addition to (dr. said rather than, but from the context; it seems 'in addition to') usual tacrolimus Led triple therapy, we need to give more therapies which mostly depend on monoclonal Abs that potentiate the regimen (tacrolimus led regimen for ex.) and targets 2 things :

1- CD3 (T-cell receptor) 2- IL-2

So what do you will give your pt. if there is a possibility of acute rejection (after the transplant in 1-8 weeks) or if the immunosuppressant drugs are not working well ? Anti-CD3 and Anti-IL-2.

- but when you use each one ?i

- If your pt is SHOWING REJECTION in the 1st 2 months you have to give him an Anti-CD3.

But from the beginning if you suspect he WILL DEVELOP REJECTION you have to give him an Anti-IL-2 as a prophylactic.

Let us talk briefly about each one :

Anti-CD3(*muromonab-CD3)*

∞ They are an Abs that bind to the CD3 on TCR which will lead to rapid depletion of the T cells in the circulation, So his immunity is suppressed now.

∞ It is used for treatment of acute rejection of renal allograft as well as for corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients.

∞ It is also used to deplete T cells from **donor** bone marrow prior to transplantation.

∞ But pay attention the problem in it is: the **initial** binding of *muromonab-CD3* to the antigen transiently activates the T cell and results in cytokine release (cytokine storm).

So, How we can deal with such problem?

Consider the cytokine storm as an inflammation, so we deal with that using anti-inflammatory drugs which include premedicating the pt. with methylprenisolone (Steroid), diphenhydramine(anti-Histamine)and acetaminophen (paracetamol =

antipyretic) to alleviate the cytokine release syndrome.

Anti-IL-2 (IL-2-receptor antagonists)

∞ more common

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

∞ We use it also to treat donor bone marrow before transplantation.
Basiliximab is an anti-IL-2 which is given as a prophylactic (20mg prior and 20mg on day 4) for acute rejection in renal transplantation *in combination with cyclosporine/tacrolimus and corticosteroid*.

∞ Main side effect is related to gastrointestinal tract (nausea, vomiting, diarrhea)
∞ it has a long half life and stays in the body for 3 months.
√ Remember in treating donor bone marrow, you can use both, because both used in depleting the T cells.

√ *And notice here, after the transplantation, in the 1st month we daily give the pt. 20mg of prednisolone, in the 2nd month we give 15, ..., in the 4th month we give 5mg, in 5th month we give 4mg,....,9th month we give 0mg; so we Decrease by 1 mg per month till 0 mg.*

So it is a glucocorticosteroid tapering to make the adrenal gland work again.

Tapering the drug is a mechanism in which the slow withdrawing of the drug occurs.'

Autoimmune Diseases = Up regulation of the immunity.

Examples:
–Rheumatoid arthritis (most common one).

–Systemic lupus erythematosus.

–Multiple sclerosis (MS).

–Insulin-dependent diabetes mellitus.

We here are interested in RA :

RA: Chronic inflammatory Disorder in which T cells produce TNF-α which activates macrophages to release IL-1, IL-6, IL-8 (will damage the chondrocytes, fibroblast and osteoblast problems, produce MMPs and other effective molecules, lead to migration of polymorphonuclear and bone and cartilage erosions).

Generally, treatment invovles mainly the Anti-metabolites drug which is methotrexate, we use it in the beginning for all pts. With a low doses in addition to the Glucocorticosteroids (because the pt. will present to you with inflammation and many other lesions) so we give him 4-6 weeks of 20-40

mg oral glucocorticosteroids(oral prednisolone) and methotrexate.

After 3-6 months we have to evaluate the pt., if he isn't responding, we add other anti-metabolites Azathioprine or chloroquine.

If all of these are not working, we give Anti-TNF-α (**infliximab**, 6months to 1year, 1 injection every month) to reduce the immunity. These injections are very expensive and the patient is immunodeficient throughout the course.

So we don't give it in the beginning, because TNF-α is involved in many Immune responses, and we don't need the pt. To be immunodeficient.

So, we keep it until the pt doesn't responding to low doses of others.

In which diseases we use anti- TNF-α ?

In refractory immune diseases: RA, SLE, inflammatory Bowel diseases (ex. Conn's disease) and all inflammatory diseases which have the same pathogenicity.

Again, the strategy is:

We give anti-metabolites to decrease the proliferation of T and B cells, if they don't work ➔ we give infliximab.

Side Effects:

- Infections will worsen to have Tb in immunodeficient pts, so even with TNF-α, we

monitor if the pt has a fever and test if there is a latent Tb, because it's a serious infection and may lead to a death.

In case if the pt has a latent Tb, we stop the injections.

- It also has immune side effects : seizure, inflammation of ocular nerve .

It's contraindicated in Congestive Heart Failure, it worsens it.

Now, if the pt doesn't respond to Anti-TNF-α, that means there is a B-cell involvement, and their % is 20%, So what drug targets the B-cell?

Rituximab (anti B cell, Anti CD20)

- Given in combination with methotrexate.

- Directed for patients who do not respond to Anti-TNF α treatments.

- Indicates the rheumatoid arthritis has a B cell component in its pathology.

Atopic Asthma Showing elevation in IgE.

Generally we treat asthma by :

1)Long term glucocorticosteroid inhalation.

2) bronchodilator (β agonist) .

If the pt. is not responding for the inhalation, we have to systemic him with oral prednisolone (at the beginning 20-40mg, 1-2 weeks) until he control his asthma, then we get him back to the inhalation .

But if the pt. is continuously living with the problem of asthma and he can't control even with systemic corticosteroid, we use Anti-IgE (oral omalizumab) which is the last hope for the uncontrolled ATOPIC asthma, this injection is very expensive.

Immunoactivators;They are Cytokines:

Ω IFN

Do you remember how we treat Hepatitis C? yes, Ribavirin and IFN α.

So they boost the immune cells and work as antiviral (IFNα,β), anticancer and immunomodulating effectors (IFN γ) .
Their side effects are: cytokines like effects: flu-like symptoms, fatigue, malaise.

Ω IL-2

Used to increase the cellular immunity in pts with cancer (melanoma, renal cell carcinoma, Hodgkin disease) and their immunity is not recognizing the cancer, so we need to boost their cellular immune system.
Side effects : fever and flu-like symptoms.

In reality, cytokines (esp. IFN-α) are better as anti-viral, but as anti-cancer; they are not effected so much, why ?

There are sths called Immune check points (Lpd1 and CTLA-4) which are molecules present normally in the body in the immune system, they have receptors on Tcells, once they bind together, they prevent tcell activation. They are crucial for maintaining self tolerance and modulating the duration and amplitude of physiological immune response in peripheral tissues in order to minimize collateral tissue damage.

To be clear, they are points of immune-inhibition (they refer to inhibitory pathway of the immune system), we need to get the balance between stimulation and **inhibition(which is the role of these check points)** of the immune system.

Now, cancer cells adapt to generate immunosuppression by misusing these points to evade the immune system clearance in particular to avoid tumor agent specific T cells response, by sending messages (Pdl1 and CTLA-4) which have receptors in the T cells to be inhibited or deactivated and stop the immune system , even when you are boosting your immunity with cytokines.

What should I do ?

Give Anti-Pdl1(lambrolizumab,newly synthesized) and Anti-CTLA4 (ipilimumab), which will bind to Pdl1 receptor and CTLA4 receptor to inhibit these check points, so we inhibit the messages that

comes from the cancer cells, so as a result we activate the immune system.
To be cleare more, cancer cells send immuno-inhibitor messages , when I inhibit them I activate immune system.
In past the cure of melanoma was 2-5%, but now with the immunomodulation which can boost the immunity the % rises to 20%.
And the % varies depending on how much the immunity is involved.
The End.

(قُلْ يَا عِبَادِيَ الَّذِينَ أَسْرَفُوا عَلَى أَنفُسِهِمْ لَا تَقْنَطُوا مِن رَّحْمَةِ اللَّهِ إِنَّ اللَّهَ يَغْفِرُ الذُّنُوبَ جَمِيعًا إِنَّهُ هُوَ الْغَفُورُ الرَّحِيمُ)

The rest is sth silly, just to help us </3

Anti-metabolites:micophenelate, azathioprine ,methotrexate : مايك الأثيوبي بلعب ترِكس

Monoclonal Abs (Muromonab-CD3 and *Basiliximab*is)
اذا ما عرف يلعب (يعني اذا صار ريجيكشن) بنخلي منى و باسل يلعبوا.

AI diseases esp.RA treatment: Anti TNF α (infliximab) هو مرض بالمفاصل، تمام ؟ فلكسي قريبة من فلكشن
اللي هي من حركات العظام مع المفاصل . ومن هون تذكروا انه علاج لل أم أس وللسيستمك .....

Anti B-cell (Retuximab)
الخلية البائية الناضجة تنتقل من نخاع العظم لليمف نود، بشو ؟ بتكسي

Atopic Asthma (Omalizumab)
تذكروا انه ما بيحل الأزمات الا البنات ، وأهمهم أمل .

Anti-Pdl1(lambrolizumab) and Anti-CTLA4 (ipilimumab).

بدالة(pdl) اللامبورغيني (نوع سيارة يا بنات ;P)
كَتلِة = قتلة (CTLA) ماما (Muma)

انا جد اسفة يا جماعة فور ذييس سيلي ذينغز، أي جست فييل