Pharmacology

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Number >>	5
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1st system - MSS

Lecture 5

In this lecture I will start talking about Autoimmune diseases in general then I'm going to talk about Rheumatoid Arthritis in specific.

*Autoimmune diseases

We are going to talk about many of them in each system we are going to study and we should note first that they have a common mechanism of action :

Mechanism of Action: [the immune cells of the body recognize something as non-self (or as a foreign body) so these cells make antigenic effect so the body will attack itself and cause damage].

- The solution for these kinds of diseases is [lowering the immunity of the body, but this will cause a very bad side effect which is **increasing the susceptibility for infections,** that's because the immune system is the bodys' defense mechanism against bacteria, viruses and other things that may cause infection.

- Those are diseases FOR LIFE, which means that you can't treat them and you only control the symptoms. So the drug that you are going to give to your patient will be a drug for life (will use it all of his lifetime) so be careful in choosing the drug and consider your patient's health condition. Mistreatment or not treating the condition is very dangerous and the results could be very unpleasant, so be careful with their medications because they are tricky :3

These are the autoimmune therapy generally, now we are going to talk about Rheumatoid arthritis only in detail and particular.

*Rheumatoid Arthritis

-It's a common autoimmune disease but it's more common in ladies (70-75% of the cases) while in men the chance is 25% only so we describe it as a ladies oriented disease.

-It causes deformities in the bone. Women who have uncontrolled Rheumatoid Arthritis have a life expectancy that's 10 years less than average (early death), meanwhile men can have a life expectancy that's less than average by 4-5 years only.

-Mechanism of action: there is a certain protein that has certain deformities, and this protein precipitates around the synovial membrane in the synovial fluid. The body will recognize this protein as non-self and this protein will be antigenic and the first cells to recognize this protein and take it are T cells and B cells:

B cells -→ take the protein and make antibodies against it (CPA) a these antibodies will walk through the body and activate T cells (The bad part is activating T cells)

T cells -→ they are phagocytes and when they're activated they will do phagocytosis and this phagocytosis will cause the secretion of : 1) TNF-Alpha

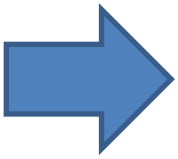
2) IL-1

3) IL-6

INFLAMMATION

Fibroblasts will be activated as well and they will cause the secretion of :

1) collagenase

2) metalloproteases  these 2 will eat collagen 2 and cause bone deformity

RANKL1 also has a role in this by binding to its receptor on the osteoclast and activating them, so now the osteoclastic activity are stronger than osteoblasts' → BONE REOSION (تآكل العظم), and this will cause bone deformities.

Note that in most cases T cells have the major role in causing the damage of this disease (80%) while the rest (20%) are from the B cells. *remember this note and pay attention to it in most cases because we are going to need it later on*.

So how can we solve this problem? by stopping the activity of T cells, since they have the major role in most cases by using DMARTs (Disease Modifying Anti-Rheumatoid Drugs) and these drugs modify the disease and won't treat it so they stop OR decrease the 3 main events that we talked about before (secretion of cytokines , secretion of collagenase and metalloproteases and activating osteoclasts by RANK). But if the disease progressed with time this will lead us to add another type of drugs that are called (BIOLOGICS) and remember them because we are going to talk about them later on.

TREATEMENT: you need to treat it FAST to decrease the deformities and “HARD” to stop the inflammation and the attack, so our main goal is [decreasing the deformities and stopping the inflammation].

All of the drugs that we are going to talk about here in treating rheumatoid arthritis are called **DMARTs**, they need time of 6-8 weeks to work. But we just said that we should treat it fast at the moment of diagnosis so what should we do? We will use a technique called Bridging Therapy, in this case give either **Corticosteroids** (Cortisone) if the patient accepted or **NSAID’s** if the patient rejected taking the corticosteroids. Some doctors give Indomethacin in this case because it’s a strong anti-inflammatory drug since it inhibits T cell and B cell proliferation but we prefer Meloxicam once daily. We give them (steroids or NSAIDs) until the DMARTs work and this is what’s called bridging therapy.

Why would a patient reject taking corticosteroids? Due to Cortisone phobia due to its side effects :

1) increasing the appetite
2) weight gain
3) water / salt retention
4) high blood pressure (hypertension)
5)thinning of skin
6) depression and mood swings
7) delayed wound healing
8) Osteoporosis
9) Onset / worsening of diabetes

*DMART’s

- We said previously that they need time to be activated so we use Bridging therapy

- They are immunosuppressants so they reduce inflammation and slow down joint destruction and preserve joint function

- Since they only control the symptoms and don’t treat them so if u stopped them the disease will come back to the patient because autoimmune disease are untreatable.

1) Methotrexate (MTX) :

- It's the drug of choice because it's the strongest one of the DMARTs

- We studied that it's an Anti-cancer drug that we used in treating leukemia (act on lymphocytes) so we use it in treating leukemia rather than solid tumors. It's more effective on T cells that's why we use it here on T cells to inhibit them (more selective toward immune cell).

- Mechanism of action: it substitutes as a folic acid and interfere with the production of tetrahydrofolate And De novo synthesis of purines

- It affect mucosal cells , hair follicles but it's more selective for immune cells so it can act on immune cells at low doses without acting on other cells but when we give it in high doses it will affect them so we can say that (hair follicles, mucosal cells and bone marrow) are dose dependent cells meaning by that they are affected by the doses . when we use it as anticancer drug we give 30mg DAILY so we notice bone marrow suppression, hair loss, diarrhea, irritation to the mucosal area but when we use it in treating Rheumatoid arthritis we give at low dose = **7.5 mg** WEEKLY because the patient will take the drug chronically (for life) and we don't want to affect his hair/bone marrow for life while in cancer he only take them for a short period. In some cases if the disease progressed we can rise the dose of 7.5 to a maximum of 25 mg WEEKLY gradually but the most important thing Is not taking it daily, only weekly to have the selectivity for T cells (immune cells) .

- After (6-8) weeks it will start working (at 7.5mg weekly dose)
- if the patient can't tolerate orally methotrexate we can give them injection of 25mg each 21 days

-Side effects:

1) it may rise liver enzymes since it interferes with purine synthesis.
2) malaise , nausea

-note : methotrexate and leflunomide are considered as X drugs because they are teratogenic so **never give it** to women during pregnancy or directly before one.

-note : methotrexate shows response in (60-70%) of patients and the rest 30% we give them methotrexate and hydroxychloroquine which we are going to talk about now.

2) Hydroxychloroquine

- It's an anti-malarial drug that is found to be useful in treating rheumatoid arthritis

- Mechanism of action : it enters the T cells then the lysosomes and the vesicles inside these cells, it rises the PH inside the lysosomes from 4 to 6, thus it will prevent the secretion of their contents (which needs low PH to be secreted out). So it stabilizes the T cells halting their reactions.

- It's not effective alone so it's an add on drug

- It affects retina causing toxicity ---> affect visual acuity , color visions and may cause difficulties in reading SO we do ophthalmic screens for visual acuity, color, vision and visual field YEARLY to make sure there's no toxicity (it causes toxicity after 5 years of usage, and remember that these drugs are used chronically).

- We use hydroxychloroquine instead of chloroquine because chloroquine has more toxicity on retina more than hydroxychloroquine but if it didn't exist and we had to use chloroquine they should do the ophthalmic tests each 6 months.

3) Sulfasalazine

- anti-inflammatory drug that consist of : Salicylic Acid that stays in the colon and Sulfa pyridine joined by : Azo Bond so it's also a pro-drug

- Sulfinpyradore: the active ingredient in treating Rheumatoid Arthritis and it's mechanism of action is not understood but the end result is inhibiting T cell activity.

- it's an add on drug to methotrexate so you either add sulfasalazine or hydroxychloroquine to methotrexate because it's not very effective alone.

- it needs 6-8 weeks to work.

-side effects : malaise, nausea, Abdominal pain, rash, headache, dizziness and note that this drug causes dizziness more than the other drugs

4) leflunomide

- In reality it is the fastest one to work and produce it's action among DMARTs although the slides say that it takes 6-8 weeks to work (like the others).

- Newly used drug that works on pyrimidine so it inhibits dihydro-orotate dehydrogenase which an enzyme that is important in de novo synthesis of pyrimidines

- DON'T USE IT WITH METHOTRXATE because methotrexate cause the inhibition of purines synthesis and leflunomide causes the inhibition of pyrimidines synthesis so this will cause bone marrow suppression

- Side effects : Diarrhea, nausea, malaise, hypertension, Rash, alopecia

NOTE THAT THIS IS THE ONLY DRUG THAT CAUSES HYPERTENSION AS A SIDE EFFECT.

5) Gold (myochrisine):

- Gold Salts not the gold used in jewelry.

- No one knows the exact mechanism, but it's nice and effective in EARLY stages of Rheumatoid arthritis

6) others :

A) Cyclosporine – will not be discussed in this course.

B) Cyclophosphamide which is an Alkylating Agent

They are common immunosuppressants

Now we are going to talk about **Biologics :**

- We use them if some patient's disease progressed and this happen in 20% of patients

- They are specially designed to treat inflammatory types of Arthritis such as:

    1) Rheumatoid Arthritis 2) Psoriatic Arthritis

- There are 20 types available (the slides says only 10 but the slides are written 10 years ago) and each type work by different mechanism than the others.

- Like DMARTs they are used to suppress the inflammation and help to prevent the damage to joints

-GOOD NEWS : they produce their activity within the first few weeks.

Some of you might now wonder , why don't use them instead of DMARTs from the first place since they do the same effect and work earlier than DMARTs ?

Because : 1) They're very very expensive so u can't use them for life

2) They inhibit the cytokines themselves and we need them for immunity.

- Current available biologics :

1) TNF-Alpha inhibitors:

A) Adalimumab
B) infliximab → they both are monoclonal antibodies for TNF and the antigenic reaction may cause rash Or anaphylactic shock

Note: infliximab dosing is irregular. You give the first dose, then the second dose will be given after 2 weeks, then after 6 weeks and then once monthly …. You then stop giving the drug in around 1 year.

C) Entracept → it's a receptor that has more affinity than the Cell's natural receptor and it's soluble so when It sees TNF- alpha it will bind to it and prevent It's binding with the cell's receptor for TNF-alpha

So since we inhibited TNF-Alpha then the patient is susceptible for infection so as soon as you notice the fever on your patient you should stop the drug and make sure that there's no infection but the DANGEROUS part is that some patients have latent TB and if it appeared it will kill the patient because the patient doesn't have immunity.

- Side effects of TNF inhibitors: 1) Infection : TB → Death

2) Neurologic → sclerosis
→ Seizures
→inflammation of ocular nerve
3) worsening of cognitive heart failure

- STOP IF FEVER DEVELOPED

2) IL-1 inhibitors : → Anakinra: (subcutaneous , 1nce daily) and since it's once daily so it's not commonly used.

3) T-cell co stimulatory blockage → Abatacept

Remember that B cells take the antigen and make antibodies that stimulate T cells and that antigen presenting cells show the antigen to T cells and bind to it through a receptor called CD80 so this type of drugs block this binding.

4) B cell depletion: → Rituximab

We previously said that T cells have the major role in causing the damages that result from Rheumatoid Arthritis but if we used DMARTs and it didn't work and we used TNF-Alpha inhibitors and they didn't work too so this means that in this case B cells have a major role (remember I previously said that in MOST CASES T cells have the major role and told you to remember this because we're going to need it later on so now this is the later on), when you figure out that the B cells have the major role, so you have to work on B cells depletion. They have a receptor called CD20 which Is important for B cells to be alive and functional so once the antibody (Rituximab) binds to this receptor then B cells will die and this cause B cells depletion.

- Note: we can also use this type of therapy in treating B cells leukemia.

this sheet was written on the honor of : ياسر عرفات

*my mom wanted me to write this *

The End