Today we will continue our subject about the antiviral drugs, we talked last lecture about
1- ***Acyclovir***, which we called it the golden drug used to treat HSV due to it's **selectivity toward the infected cell only**, by activity against the viral **kinase only**. It also **has few side effect** specially that it doesn't cause a serious immune suppression unlike the other anti metabolite drugs.

** **Note** :
Viruses don't usually infect normal healthy person, they infect immune suppressed pt. that's why treating a viral infected person who is already immune supressed with a drug that cause further immune suppression will cause a huge problems .

Where will we see ***Acyclovir***?

1. Prophylactically in patients treated with immunosuppressant drugs or radiotherapy who are in danger of infection by reactivation of latent virus.

2. Herpes simplex infections (oral labialis, genital herpes, and herpes encephalitis).

3. Chickenpox in immuno-compromis patient.

4. Prophylactically in patients with frequent recurrences of genital herpes (especially in western countries not here).

5. Treatment of HSV usually doesn't cure or stop the disease but will *reduce the period of the disease (reduce the symptoms by one to two days) .*

- in prophylactic cases we use half the dosetwice a day maybe for six months

- ***Topical Acyclovir*** (cream, ointment) is substantially less effective than oral therapy for primary HSV infection. It is of no benefit in treating recurrent genital herpes. It has some activity in oral labialis .

some side effect of Acyclovir :-

Normal side effect; nausea, vomiting, diarrhea and the most important one is the headache in 5% to 10% but it will resolve within one to two days.

Acyclovir maybe toxic and looks like " Cisplatin " when taken **IV** it may precipitate in the kidney causing renal insufficiency or may affect some neurons.

These effect may appear during treatment of herpes encephalitis when we need to use high doses during treatment , but we can overcome these side effect specially the renal one by avoiding rapid infusion of the drug and adequate hydration of the patient by saline .

- In oral treatment there won't cause renal toxicity or renal insufficiency.

Now we will move to another drug which is considered (OTC) over the counter drug that is ***Docosanol :***

we use it to reduce the symptoms of the disease , ***not really useful and has no real medical benefits.***

Another drug now that is used to treat another type of viruses (CMV) is called

Ganciclovir :

CMV is not causing any problem in normal people , but in immunocompromised patient like those who have cancer and undergo cancer therapy or kidney transplant it is considered a major problem that we need to prevent those patient or sometimes treat in another patient , so *it is not used that much in normal hospitals mainly for immune-compromised* .

CMV can cause:

1. Retinitis (we give the drug topically)
2. Pneumonia (we give the drug IV)
3. Colitis (we give the drug IV)

What is the difference between ***Ganciclovir*** and ***Acyclovir***?

The ***Ganciclovir*** has an additional " **OH** " group which makes it ***more selective toward CMV***, and it is 100 times more selective than ***Acyclovir*** in treatment of CMV
- the Dr said it is used to treat CMV = Cyto" MEGA " lovirus , make mega as a reminder of 100 - .

Although it is more potent but we start treatment by using ***Acyclovir*** not Ganciclovir, why?

Because it is not 200% selective against the viral kinase, it is only 10% more selective toward the HSV infected cell more than the normal cell (much less than the ***acyclovir***) and this leads us to problem of immune suppression which is the major side effect of Ganacyclovir .

- Most common adverse effect:

bone marrow suppression (leukopenia 40%, thrombocytopenia 20%) and ***CNS effects*** (headache, behavioral, psychosis, coma, convulsions).

- we treat the patient IV infusion for 21 days then we follow it with 1000 milligram/day as oral treatment and the whole treatment for CMV is usually for two months.
- 1/3 of the patients have to stop because of adverse effects.

- If the patient is in a life threatening situation and the viral load is really high we will start with Ganaciclovir even though it has these side effects

- Low oral bioavailability and when it is given orally it looks like ***Acyclovir*** that's why it is usually given IV , However we can use a drug called ***ValGanciclovir*** which has the same effect of ***Ganciclovir*** *but with much higher bioavailability*

What will we do if the patient is resistant toward the ***Acyclovir*** and doesn't respond (and this is not uncommon - it is found in almost 20% of cases) and also toward the ***Ganciclovir***?

In these cases we will use another drug with different mechanism of action other than the antimetabolite, this drug is called " ***Foscarnet*** ":

- An inorganic pyrophosphate analog

- Active against Herpes (I, II, Varicella, CMV), including those resistant to ***Acyclovir*** and ***Ganciclovir***.

- it is directed against **DNA polymerase** causing inhibition to it but again and again, we don't start treatment using it due to *vey bad side effect ;* immunosuppression and high incidence of nephrotoxicity (25% and here hydration has no benefits)

when do we use ***Foscarnet*** ?!

(1) CMV retinitis and other CMV infections instead of ganciclovir

(2) H. simplex 1,2, varicella and CMV resistant to ***Acyclovir and Ganaciclovir***.

(3) HIV. (Because it also inhibits to the reverse transcriptase)

Vidarabine :

Vidarabine has only one use, as eye drops against *vaccinia keratitis*.

What is vaccinia?
it is a type of virus used in ***vaccines***, sometime the virus isn't too latent so after injecting the patient with vaccinia he will develop ***kertitis*** and sometimes it will be in the form of ***keratoconjictivitis .***

so we use ***topical vidarabine***, one of the drugs used, in these cases .

It is an anti-metabolite drug , as ***acyclovir***, but totally ***non selective*** and it is an ***immunosuppressant.***

Its use is now limited to ***topical treatment of severe herpes simplex infection***. Before the introduction of the better tolerated ***acyclovir***, vidarabine played a major part in the treatment of herpes simplex encephalitis. " *Dr.Malek said that this isn't required from us because we won't see it ."*

Lets move to the interesting subject!!

Influenza(A,B)

common disease that affect most populations in the world

five drugs that has been FDA-approved to treat the virus,
1)three are neuraminidase inhibitors
2 two are called infusion inhibitors that are no more used due to the fact that most influenza species developed resistance to them, they are ***Amantadine and Rimantadine*** .

The most drugs used are :

1) Oseltamivir : which is called ***Tamiflue***, it is an oral drug taken 5mg twice daily
2) Zanamavir, it is an inhaler also dosed 5mg twice daily .

→ Note : they are also used as prophylactic for immune-compromised patient by half the dose

Who should be treated by these drugs, mainly oseltamvir ?!:

1- life threatening cases:
in such cases the patient may have predisposing diseases or factors such as COPD where the infection will cause exacerbation of his condition .

2- if he is old above 60 years (geriatrics) or an infant less than 1 or 2 year .

3- immune-compromised patients .

Why we don't use ***oseltamavir (Tamiflue***) usually ?

Simply, for the same reason why we don't use ***Acyclovir*** against oral labialis .
These drugs only reduce the duration of the infection 1-2 days.

If you want to prophylact a patient we usually use half the dose that is used to treat the diseased one

In clinic there is a big issue, WHO always is trying to avoid the high use of these drugs *in order not to lose them*, because they are the only active drugs against influenza virus
are the *Neuroamindase inhibitors****; zanamavir, oseltonavir***, and a new IV drug called ***verabavin*** from the same group.

about this drug, it was approved by FDA in 2009 pandemic of the swans flue and then we stopped it due to the lack of enough clinical data to grantee its safety, until 2014 when it was approved in the market

.

Do we need anti-influenza drug IV?!
Yes, in serious conditions mainly and in the conditions mentioned above.

Can it kill the patient ?
yes, these 3 groups.

and these drugs *aren't used in community*, in order not to lose them and because of the ***cross resistance*** where we will lose the activity of all these drugs

How to prophylact your body ? take the vaccine .

Now lets move to the mechanism of action of those drugs

Viral neuraminidase catalyzes cleavage of terminal sialic acid residues attached to glycoproteins and glycolipids, a process necessary for release of virus from host cell surfaces. Neuraminidase inhibitors thus prevent release of virions from infected cell.

we are **inhibiting the release.** So if there were releasing the drug will not be effective , so we have to start the treating of influenza infection within the first 8 hours because if we are starting after the 8 hours we are passed by the time of spreading of the Virus. (We take it prophilactily).

→How the drug is effective ?!
By reducing the symptoms and severity of the flu by one to two days.

→Do I usually prescribe Tamiflue ?!
No because it costs (33JD)

→**Note** some patient don't respond to ***zanamavir***.

Toxicities :

– Exacerbation of reactive airway disease by ***zanamavir*** (not indicated for COPD patient)

– Nausea and vomiting for ***oseltamivir***.

●Notes regarding ***oseltamivir*** :-

→ Early administration is crucial because replication of influenza virus peaks at **(24–72)** hours after the onset of illness. When a 5-day course of therapy is initiated within 36–48 hours after the onset of symptoms, the duration of illness is *decreased by 1–2 days compared with those on placebo*,

→ severity is diminished, and the incidence of secondary complications in children and adults decreases.

→ Once-daily prophylaxis is 70–90% effective in preventing disease after exposure.

Anti retroviral agents:

We never use a single drug in treatment of AIDS, we have to use multiple regimen for AIDS, We call it high effective anti retroviral therapy

We treat AIDS similar to other viruses but we have different targets:-

1- Fusion inhibitors
2- Reverse Transcriptase inhibitors
3- Integration inhibitors
4- Protease inhibitors
5- Budding and releasing inhibitors

Why do we use different drugs ?
High mutation frequency and high incidence of resistence.

Treatment is really effective but really expensive

Anti retroviral agents:-

1) Azidothymidine [Zidovudin(AZT)]:

1) It's the prototype
2) Antimetabolite immunosuppression
3) Non-selective
4) the main drug in which the treatment is based.

2) Non nucleotide reverse transcriptase inhibitor :

1) It's **NOT** an antimetabolite (it's not introduced to the chain and it does not stop the elongation, it's directed toward reverse transcriptase just like the one we mentioned before (***Foscarnet***)
2) It's the **second choice** to be used to attack the infected or viral cells or the AIDS.
3) They have to be *combined with other drugs* because it's common to **develop resistance** if used alone, just like the first drugs [nucleotide like reverse transcriptase inhibitors (Antimetabolites)].

Nevirapine:
* It has a very good activity in ***inhibiting the vertical transmission for HIV*** (From the mother to the child).
* Single dose at delivery reduced HIV transmission by **50%**
we use the above mentioned ***Zidovudine*** alongside ***Nevirapine*** •
prophylactically against the vertical transmission.

- ***NNRTI*** side effects:

1) Rash:

In order to decrease the incidence of the rash we escalate the dose over 14 days
.
→What does **escalation** the dose of the drug mean?!

In escalation **we increase the dose gradually** in order not to get a side effect that may be caused if a high dose was given from the beginning.
It's just like **tapering** the dose but the difference here is that in tapering the dose of the drug we decrease the dose of the already given drug gradually in order to decrease or inhibit a side effect that may be caused due to a sudden usage of the drug just like steroids

2) CNS effects

3) Protease inhibitors:-

- One example is ***Saquinavir*** and it may be combined with the two above-mentioned drugs.
→ We have two problems with protease inhibitors:

1) Drug-drug interaction: The protease itself has some homology with cytochrome P450 in humans, so these protease inhibitors may interact with and inhibit the action of cytochrome P450, thus interacting and interfering with so many other drugs since those drugs (the other drugs) need cytochrome P450 to be metabolized.

2) Buffalo hump; the dr said it's not of that important.

4) New Targets:

- ***Raltegravir*** is a new drug we add it to the ***HAARTs***
We use it to protect the non-viral cells (non-infected cells) from being invaded by the virus from a nearby infected cell (*be aware it's not a prophylactic drug*).

5)HAARTs(*Highly active anti-retroviral therapies****) :-***

- Highly active anti-retroviral therapies.
- Regimen-containing HAARTs is *very effective* and can *reduce viral load in the patient* below detectable levels implying that HIV replication has ceased (the patient may live up to 15 years in a good condition).

- Two types :

1) PI-Based Regimens (1 or 2 PIs + 2 NRTIs)

2) NNRTI–Based Regimens (1-NNRTI + 2NRTIs)

- we treat using combination therapy as we combine different strategies that are already

mentioned (PIs + NRTIs + NNRTIs) and since 2005 we added ***Integrase Inhibitor*** to these combinations.

- **Compliance** is one of the major issues in using these drugs. If the patient didn't take this drug continuously, the incidence of the resistance will be increased and the high mutation rate will affect their life.

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- **Non-compliance** with protease inhibitor therapy is of serious concern as the new virus that emerges is resistant to the inhibition being taken and also resistant to other protease inhibitors.

Hepatitis B and C:

We take vaccine for hepatitis for A & B .But for hepatitis C there is **No vaccine** and it is the worst type; because 50% of those who are infected with hepatitis C are subjected to chronic liver diseases (cirrhoses , hepatocarcinoma).

Hepatitis B: (10 % - 15 %) they get hepatitis B **latent** which means there is **no symptoms** but the may develop hepatic carcinoma.

Hepatitis A: it is just an infection may take from 2-6 months (long infection) But treatable and do not stay with the patient.

Hepatitis A → do not stick with the patient and treatable
Hepatitis B & C → stick with the patient and we have to reduce the load of the virus.

→How do we treat **Hepatitis B?!**
We usually do not treat hepatitis B positive patient, because there is no sign or symptoms. But sometimes there is signs and symptoms in 1% of the patient so we give them drugs (they are anti- metabolite) they will inhibit polymerase .

→How do we treat **hepatitis C?!**
we use in this case **combination therapy** for 6 months (24 weeks)
we combine 2 drugs :
1) Interferon 2α they have to take the injection once daily for 6 months, We introduced anew type of interferons called Pegylated interferons ,which we inject once per week for 24 weeks.

Note : interferons is nonselective anti viral biologics it is already exist in our bodies to fight viruses so we give this drug to augment the immune system to fight against this virus.

*Interferon, mechanism of action:

• 1) binds to cell surface receptors

• 2) induces expression of translation inhibitory protein (TIP)

• 3) TIP binds to ribosome, inhibits host expression of viral proteins

Disadvantages: include a high rate of treatment-related adverse events. **flu-like symptoms**: increased body temperature, feeling ill, fatigue, headache, muscle pain

2) Ribavirin : which is also used in inhibition of influenza RNA Polymerase
Ribavirin has side effects but they are not very common (Anemia)

Done by:

●Mohammad Abu dosh
●Tareq Al-Tal
●Saif Abu baker
●Mohammad dmour
●Faris khamaiseh

Corrected by : Ra'ad Al-Muhaisen