بسم الله الرحمن الرحيم

Treatment of viral hepatitis

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no eradication of hepat.---•
but cure yes.
so :-
cure : فيروس موجود داخل جسمي
لكن مابتأثر
ممكن ما نزلت مناعة الشخص لأي سبب رح يرجع يتأثر الفيروس.

REMEMBER THE FOLLOWING ABOUT ANTIHEPATITIS DRUGS

- They are not curative
- They suppress **Viral replication**, put patient in remission, prevent complications.
- Have to be taken for long duration
- Disease can flare up when drugs stopped
  reactivation

Hepatitis B : DNA virus
" C : RNA virus

- Most drugs are nucleoside/nucleotide analogues (purine + pyramidine)
  All these drugs same mechanism of Action.
- Most are prodrugs
- Most are converted to phosphate form
- Most inhibit (DNA polymerase/RNA polymerase)
  حسب نوع اعادة الوراثة للفيروس.

Drugs treating HBV infection

1- Lamivudine and Telbivudine

not first line Tx due to rapid resistence
oral

- Cytidine Nucleoside analogue

MOA

هاي الدوية بس تدخل جوا الجسم لحتى الهاوشوة يعني تتحول من mono into → tri phosphate

Phosphorylated intracellularly.

Inhibits **HBV DNA polymerase**. Causes viral DNA chain termination by getting incorporated into viral DNA. not RNA

Use

1. **Chronic HBV infection – 100mg OD**
   - ✓ Brings about clinical, biochemical , histological improvements but effects not sustained over the years. → moderate not severe so not first line
   - ✓ Development of resistance within 1-5yrs → **NOT THE FIRST LINE DRUG**
2. **HIV - 150-300mg OD** (in combination with other anti HIV drugs)

Pharmacokinetics

- Good oral bioavailability
- Plasma T1/2 = 6to 8hrs (t1/2 = 12hrs in HBV infected cells) so → بعطيه مرتين باليوم
- Excreted unchanged in urine → so no Drug-Drug interaction

ADR

(*Well tolerated*)

- Headache, fatigue
- Nausea, anorexia, abdominal pain
- Rashes
- Pancreatitis, neuropathy (rarely)

- ❑ Genetic mutations of HBV DNA polymerase causes resistance to lamivudine.
- ❑ Telbivudine is superior to lamivudine in treating HBV.

2- Entecavir

Guanosine nucleoside analogue with same MOA as Lamivudine

Differences from Lamivudine

- Food decreases oral absorption(administered in empty stomach)
- T1/2 : 128-148hrs
- Sleep disturbances & lactic acidosis can be additional ADRs
- 1st line drug for HBV ?
  - ① Rapid clinical, biochemical, histological improvement than Lamivudine
  - ② Effect sustained
  - ③ Development of resistance rare

3- Adevofir dipivoxil

AMP nucleotide analogue.

Prodrug. Gets activated to Adefovir (by esterases in intestine & liver). MOA same as Lamivudine.

Uses

1. Chronic hepatitis B
   - **Not a 1st line drug** as virological response is slow.
   - Used mainly in lamivudine resistant cases

4- Tenofovir Disoproxil fumarate

Nucleotide analogue Prodrug converted to Tenofovir.

Similar to Adefovir but it is **first line drug for HBV** due to its High efficacy, good tolerability & low risk of development of resistance,

Has activity against HIV also (reverse transcriptase inhibitor)

Drugs for HCV

RNA polymerase not DNA polymerase

1- Ribavirin

Broad

مريت باليوم

- Guanosine nucleoside analogue
- **Broad spectrum antiviral drug**
  - HCV
  - Influenza A & B
  - Respiratory Syncytial virus (RSV)

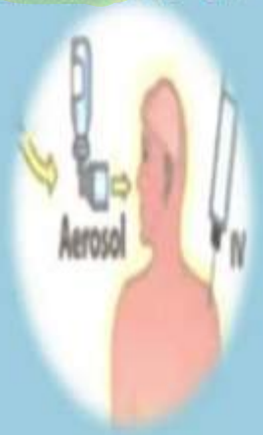
MOA

Phosphorylated inside cells → like others

Inhibits RNA polymerase & stops viral RNA replication.

Uses

1. Chronic Hepatis C (in combination with interferons or other drugs) (6-12 months) فترة علاج سنة تقريبًا



2. RSV Bronchiolitis in children (nebulisation)

by Route : inhalation exam

ADR

exam

- Hemolytic anemia (dose dependent)
- Bone marrow suppression
- CNS/GIT effects (stimulation)
- Teratogenic (Females to practice contraception during & till 3months after Ribavirin treatment) يوقف أخذ هذا الدوا قبل شهور ثم يحبن can pregnant ←

2-Interferon (IFN)α

WHAT ARE INTERFERONS ?

Low molecular weight glycoprotein cytokines produced by host cells in response to viral infections, IL-1 & other inducers.

They have antiviral effects & effects on immunity & cell proliferation

3 types of IFN produced by humans — IFNα (Clinically used)
IFNβ
IFN γ

PEG-IFN resulted in a **sustained loss of hepatitis B e antigen** (Hbe Ag) in 30% of patients.

Pharmacokinetics of interferone:

-INF is ineffective orally and given by I.M. or S.C. route.

-They are inactivated in the body fluids and different tissues including kidney.

-Only small amount is excreted by the kidney.

exam

- *Pegylated interferon*: attachment of IFN proteins to large, inert polyethylene glycol molecules (pegylation) slows the absorption, decreases the clearance, and provides higher and more prolonged serum concentrations that enable once-weekly dosing.

- Two pegylated interferons are available commercially: *peg-interferon alpha-2a* and *peg-interferon alpha-2b*.

بداية كان كورس آخذ هام كل لام
بس بحدين صرنا نضيف عليهم
مادة عمتان تقلل من امتصاصهم
فورنا نعطيهم مرة وحدة كل اسبوع.

Uses of pegylated interferon alpha:

1-Its role in treating hepatitis B and C is limited now (mainly for HBV e positive Ag).

2- As adjunctive treatment in certain tumors as non-Hodgkin's lymphoma, hairy cell leukemia, , multiple myeloma, and AIDS-related Kaposi sarcoma.

3-It is used in treating Genital warts (condyloma accuminata) caused by Human papilloma virus; and in severe cytomegaloviral and herpes zoster infections..

Mechanism of Anticancer is: Immune active

Adverse effects:

a) Influenza-like illness (fever, chills, headache, myalgia, nausea and vomiting).

b) Bone marrow depression.

c) CNS: confusion, **seizures** and behavioral changes. → CNS stimulation

d) Renal toxicity and cardiac toxicity.

e) With chronic use: anorexia, fatigue, weight loss, development of antibodies that decrease the antiviral activity.

It is contraindicated in cardiac patients and during pregnancy

3- Direct acting anti-HCV drugs (DAA)

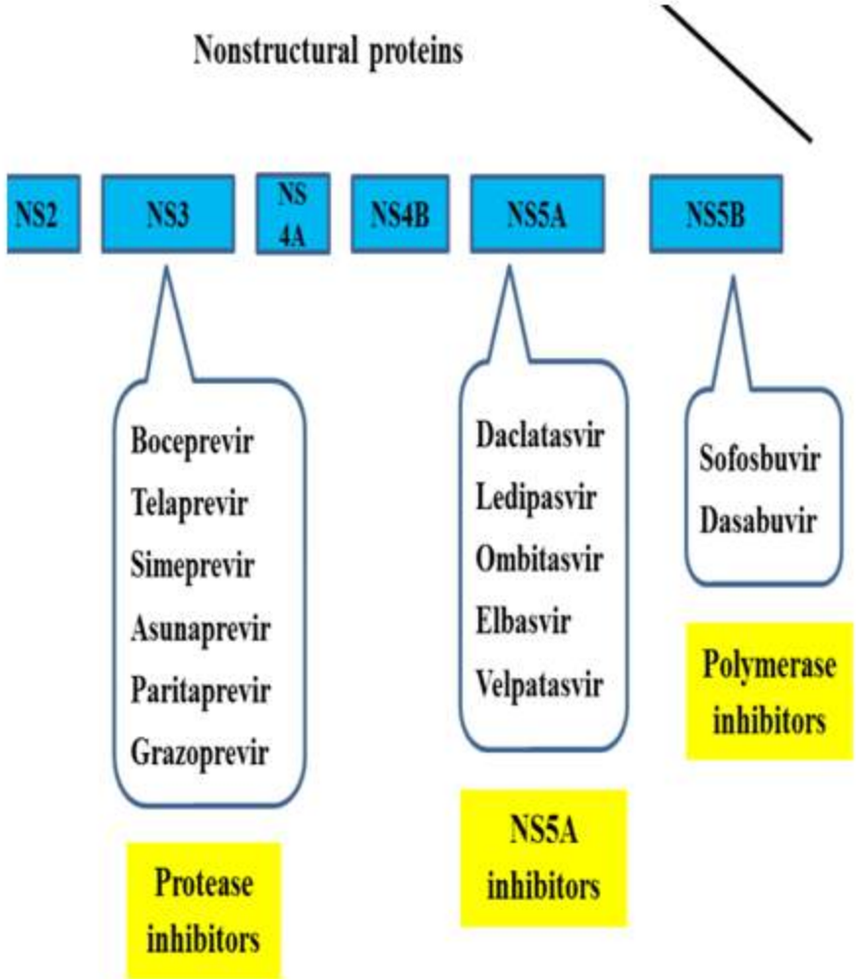
first line Treatment of hepatitis C.

- Target specific nonstructural (NS) viral proteins that play role in replication of HCV inside hepatocytes.
- Less efficacy & development of resistance on using as monotherapy

- Used in combination therapy against HCV
  - Shortens duration of therapy
  - Improves clinical response.
- Minimal ADRs

- Significant drug interactions due to metabolism for these drugs by CYP3A4

Metabolism and excretion



Sofosbuvir (Sovaldi)

Mechanism of action:

-Sofosbuvir is a pro-drug & converted to triphosphate active form, which inhibits HCV RNA polymerase, resulting in inhibition of RNA synthesis.

✓ Little resistance develop to sofosbuvir.

Pharmacokinetics

-Sofosbuvir is used only **orally**.

-T ½ of sofosbuvir is 0.4 hour, but its metabolite has t1/2 = 27 hours (once daily dose).

Therapeutic uses

❑Sofosbuvir is used in combination with other oral direct acting antiviral drugs as **first-line treatments for HCV.**

✓ **Sofosbuvir** in combination with velpatasvir is recommended for **all genotypes** with a cure rate greater than 90%. The duration of treatment is typically 12 weeks.

- ☐ for HCV genotypes 1, 4, 5, and 6 (**sofosbuvir** with **ledipasvir**).
- ☐ For HCV genotype 2 and 3 (**sofosbuvir** with daclatasvir).
- ☐ For HCV with **cirrhosis or liver transplant patients**, **ribavirin** is sometimes added.

- ➢ Peg-interferon with or without sofosbuvir is no longer recommended in an initial HCV treatment.
- ➢ Compared to previous treatments; sofosbuvir-based regimens provide a higher cure rate, fewer side effects, and a two- to four-fold reduced duration of therapy.

Side effects

- **Fatigue**, headache, nausea, rash, irritability, dizziness, **back pain**, and anaemia are the common side effects .
- -Sofosbuvir may reactivate hepatitis B in previously infected patients.
- Safety during pregnancy is unclear; some of the medications used in combination may result in harm to the baby.
- Sofosbuvir **increases the toxicity of amiodarone** with unknown mechanism.

Drug interactions of DAA drugs

- All are metabolised by CYP3A
- All are substrates of P-gp efflux transporter

CYP3A inducers/ inhibitors decrease their effect/increase their toxicity

Inducers of P-gp (Phenytoin/rifampicin) decrease their blood levels

Ledipasvir, Velpatasvir need gastric acid for absorption. Their efficacy decreased by H2 blockers