بسم الله الرحمن الرحيم

Pharmacology
Drug treatment of viral hepatitis

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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

- Most drugs are nucleoside/nucleotide analogues
- Most are prodrugs
- Most are converted to phosphate form
- Most inhibit DNA polymerase/RNA polymerase

Drugs for HBV

- ✓ Lamivudine (3TC)
- ✓ Telbivudine (LDT)
- ✓ Entecavir -ETV(**first line**)
- ✓ Adefovir dipivoxil(ADV)
- ✓ Tenofovir disoproxil fumarate (TDF) (**first line**)

Drugs for HCV

- ✓ Ribavirin
- ✓ Interferon alpha

Newer Drugs (Directly acting antiviral drugs)

- ✓ NS5B polymerase inhibitor : Sofosbuvir
- ✓ NS3/4A protease inhibitor : Simeprevir
- ✓ NS5A inhibitor : Daclatasvir, Ledipasvir, **Velpatasvir**

Drugs treating HBV infection

1 Lamivudine

➢ Cytidine Nucleoside analogue

MOA

Phosphorylated intracellularly.

Inhibits **HBV DNA polymerase**. Causes viral DNA chain termination by getting incorporated into viral DNA.

Use

1. Chronic HBV infection – 100mg OD

✓ Brings about clinical, biochemical , histological improvements but effects not sustained over the years.

✓ 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)
- Excreted unchanged in urine

ADR

(***Well tolerated***)

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

- ❑ N.B. Genetic mutations of HBV DNA polymerase causes resistance to lamivudine.
- ❑ N.B. 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**

- Rapid clinical, biochemical, histological improvement than Lamivudine
- Effect sustained
- Development of resistance rare

3 Adefovir 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 acting on HCV

Ribavirin

- Guanosine nucleoside analogue

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

MOA

Phosphorylated inside cells

Inhibits RNA polymerase & stops viral RNA replication.

Uses

1. **Chronic Hepatis C** (in combination with interferons or other drugs) (6-12 months)

2. **RSV** Bronchiolitis in children (nebulisation)

ADR

- Hemolytic anemia (dose dependent)
- Bone marrow suppression
- CNS/GIT effects
- Teratogenic (**Females to practice contraception during & till 3months after Ribavirin treatment)**

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:

-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.

- ***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: *peginterferon alpha-2a* and *peginterferon alpha-2b*.

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..

Adverse effects:

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

b) Bone marrow depression.

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

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

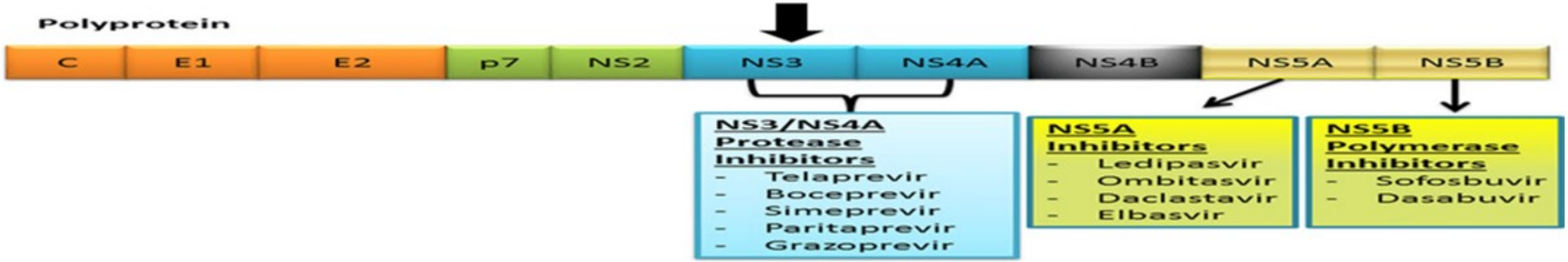
Direct acting anti-HCV drugs (DAA)

- 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



Sofosbuvir (Sovaldi)

-Sofosbuvir must be given combined with other drugs for treatment of HCV.

-Cure rates are 30 to 97% depending on the type of hepatitis C virus.

Mechanism of action

-Sofosbuvir is a nucleotide analog.

-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**.

-Sofosbuvir is activated in the liver to the triphosphate (active form) then finally metabolized to inactive metabolite.

-The half-life of sofosbuvir is 0.4 hours, and the half-life of metabolite is 27 hours which allows once daily dose.

Therapeutic use

-sofosbuvir is used in combination with other drugs in all 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 the treatment of **genotypes 1, 4, 5, and 6 hepatitis C** infections, sofosbuvir can be used in combination with **ledipasvir**.
- ❑ In **genotype 2 and 3 HCV infections**, sofosbuvir can be used in combination with **daclatasvir**.
- ❑ For the treatment of cases with **cirrhosis or liver transplant patients**, weight-based **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

- - Sofosbuvir has a good safety profile if used alone and in combination with other drugs.
- - **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


THANK YOU