LTBI ⇒ 3 / 9 Months

→ 9 Months isoniazid mono

OR → 12 once-weekly doses of Isoniazid (900 mg) + Rifapentine (900 mg)

(3 Months)

Active TB ⇒ 6 Months

→ Isoniazid 6 Months
Rifampin 6 Months
Pyrazinamide 2 Months
Ethambutol 2 Months.

MDR-TB ⇒ 2 years

** XDR-TB → Linezolid
Clofazimine

* I, F, P → Bactericidal
↔ Bacteriostatic

First line Treatment

ISONIAZID

- MOA:
  prodrug → Activated by KatG (Mycobacterial Catalase-Peroxidase)
  ⇒ target InhA & KasA
  ⇒ inhibits synthesis of Mycolic Acid
- sPecific for M. Tb → against intracellular organisms.
- Resistance:
  Chromosomal Mutations:
  1) deletion of KatG
  2) Acyl carrier proteins
  3) overexpression of InhA.
- Isoniazid / Ethionamide → Cross-resistance
- Pharmacokinetics:
  - oral
  - impaired absorption w/ food (high fat)
  - all body cells & fluids & caseous Material.
  - [CSF] = [Serum]
  - N-Acetylation / hydrolysis ⇒ inactive.
  - ← Metabolites in urine
- At:
  - Hepatitis (↑Incidence w/ Age & Alcohol) >35 y.o.
  - peripheral Neuropathy ⇒ 25-50 mg Pyridoxine (B6) takes
  - CNS → convulsions, seizures.
  - Hypersensitivity → rash / fever.
  - inhibits Metab. of Carbamazepine & phenytoin ⇒ ↑ their AE (Nystagmus / Ataxia).

RIFAMPIN

(Rifampin, Rifabutin, Rifapentine)

- Broader Antimicrobial spectrum ⇒ several Bac infections.
- ~~ATSMD~~ NEVER Monotherapy ⇒ bc Resistance.
- MOA:
  block RNA transcription.
  (β subunit of DNA-dependent RNA polymerase)
- Spectrum:
  bactericidal (intra & extra-cellular)
  M Tb / NTM
  G(+) & G(-)
  Prophylactically @ Meningitis Exposure.
  M. leprae.
- Resistance:
  Mutations @ RNA pol. affinity
- Pharmacokinetics:
  - oral
  - all body fluids + organs
  - [CSF] = 10-20% [Blood]
  - induce cyt p450
  - "Autoinduction" ⇒ shorter t½ 1-2 weeks.
  - bile, faeces > > > urine.
  - urine, faeces, tears, contact lenses ⇒ orange-red colour
- At:
  - N/V/Rash.
  - Hepatitis / Liver failure ⇒ Rare.
    ↳ but ↑ w/ isoniazid.
  - intermittent dose ⇒ flu-like syndrome (>1.2g)
    ↓
    Acute Renal failure, Haemolytic Anaemia + Shock
  - induces cyp450 phase I & II enzymes ⇒ shorter t½ of other drugs.
    ⇒ 1. Toxicity of coadministered drugs
    2. change drug to one less affected
    3. Replace Rifampin w/ Rifabutin.

PYRAZINAMIDE

- synthetic
- MOA: unclear.
  (prodrug)
  pyrazinamide —Pyrazinamidase→ Pyrazinoic Acid.
- Resistance: strains lack Pyrazinamidase
- Against: TB in
  1) Acidic lesions.
  2) Macrophages.
- Pharmacokinetics:
  oral
  throughout body + CSF
- At:
  liver toxicity!
  uric Acid Retention (gouty attacks rare)
- Clinical ~~tx~~ benefit early

ETHAMBUTOL

- BACTERIOSTATIC, Specific
- MOA:
  inhibits Arabinosyl transferase (imp @ synthesis of cell wall)
  can be
- Discontinued if isolate is susceptible to R, I, P
- Pharmacokinetics:
  - well distribution throughout body.
  - CNS penetration Minimal
    (Questionably Adequate for TB Meningitis)
  - urine excretion.
- At:
  - optic Neuritis ⇒ diminished visual Acuity ⇒ Red-green colourblindness. (imp)
    (↑ risk @ higher doses & Renal impairment)
    [test before tx & periodically after]
  - ↓uric Acid excretion
    ⚠ ppt w/ Gout.

RIFABUTIN

- @ HIV co-infection. who are Receiving PIs & NNRTIs
- Less potent inducer (40%) of Cyt P450 ⇒ ↓ drug interactions.
- At:
  same as Rifampin + uveitis, skin hyperpigmentation, Neutropaenia

RIFAPENTINE

- higher Activity than Rifampin
- longer t½.
- w/ Isoniazid @ HIV(-) ppt or LTBI ⇒ 1 / week
  (↓ w/ Minimal pulm. TB)

Second line Treatment

STREPTOMYCIN

<Aminoglycoside>

- was 1st effective agent against TB.
- Action greater against Extracellular
- Streptomycin - Resistant
  ⇒ **Kanamycin**
  Amikacin.

Para-AMINO SALICYLIC ACID (PAS)

- one of original TB Meds.
- 1950s → 1960
  Standard 18-Month Tx was PAS + Streptomycin.
- Largely replaced by Ethambutol but remains imp @ Many MDR-TB Regimens.

CAPREOMYCIN

- Parenteral
- inhibits protein synthesis.
- Reserved for MDR-TB.
- careful Monitoring Necessary to Minimise:
  - Nephrotoxicity
  - Ototoxicity.

CYCLOSERINE

CNS ↑ seizures ↑ Ser/Ala ⇒ DAA

C/S → static → CSF

- Oral
- Bacteriostatic
- MOA: disrupts D-Ala incorporation into cell wall.
- pharmacokinetics:
  - thruout body fluids & CSF
  - urine excretion (unchanged)
- { Renal insufficiency ⇒ Accumulation }
- AE:
  - CNS disturbances { lethargy, difficulty concentrating, Anxiety, suicidal tendencies } 2me.
  - seizures.

ETHIONAMIDE

- Structural Analogue of Isoniazid
- MOA: disrupt Mycolic Acid Synthesis. { Not identical to Isoniazid, but Resistance overlap }
- pharmacokinetics:
  - widely distributed + CSF
  - Extensive Metabolism esp. @ Liver { to Active & Inactive }
- AE:
  - N/V
  - Hepatotoxicity
  - hypothyroidism, gynecomastia
  - gynecomastia
  - Alopecia
  - impotence
  - CNS effects.

MOXIFLOXACIN & LEVOFLOXACIN

<FLUOROQUINOLONES>

* MDR-TB (imp).
- some (NTM) are susceptible.
- QT prolongation + Tendon Rupture.

AZITHROMYCIN & CLARITHROMYCIN

<MACROLIDES>

- @ Regimens of several NTM.

→ Azithro: preferred for patients @ greater risk for drug interxn

Clarithro: substrate & inhibitor of Cyt P450

BEDAQUILINE

- MOA: ATP-Synthase Inhibitor
- 1st in a new class of drugs for MDR-TB
- Oral
- Many types of Mycobacteria.
- AE:
  - QT elongation
    ↳ ECG Monitoring.
- CYP3A4 substrate
  ⚠ admin. w/ CYP3A4 inducers.