CLINICAL MANAGEMENT OF DRUG INDUCED LIVER INJURY IN TB/HIV PATIENTS ON BOTH ART AND ANTI-TB DRUGS

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Presentation outline

① Definition of DILI
② Background
③ Mechanisms of DILI
④ Management of DILI
DILI diagnosis

- ALT or AST > 120 IU/L and symptomatic (nausea, vomiting, abdominal pain and jaundice)

  OR

- ALT or AST > 200 IU/L

  OR

- Total serum bilirubin concentration > 40 μmol/L
DILI is a common adverse drug reaction in TB treatment 5 to 30%
The risk increase for TB/HIV treated patients 10 – 35%
South Africa mortality of DILI was 27 – 35%
Background..

Drug Induced

- Primary compound
- Metabolite
- Immunological mediated response

Liver Injury

- Hepatocytes
- Biliary epithelial cells
- Liver vasculature
Predictable DILI (dose related and occurs rapidly)

Injurious free radicles - Liver necrosis

Idiosyncratic/unpredictable reaction
  – rare, hypersensitivity / portal inflammation
Mechanisms of anti TB drugs

**Rifampicin**

- Dose depended DILI/block bilirubin uptake
- Unconjugated hyperbilirubinemia
- Jaundice without hepatocellular damage

**Pyrazinamide**

Both dose dependent and Idiosyncratic hepatotoxicity

**Isoniazid**

- Metabolite (Acetylated INH)
- Produce free radicles
- This occurs within weeks or months
Mechanisms DILI with ART

**NRTI**
- Mitochondrial toxicity
- Hepatic steatosis

**NNRTI**
- Hepatotoxicity
- Severe transaminitis
- NVP- associated with rash + fever

**Protease Inhibitor**
- Mechanism of action not known
- Suspect – impaired drug metabolism
Differential diagnosis of DILI

ART may result in enhanced immune response to TB, HBV, HCV

**TB IRIS**
- Obstructive picture
- IRIS in other organs

**HBV IRIS**
- Hepatocellular injury

**HIV/TB**
- TB itself – Liver disease
- TBIRIS
- Bacterial sepsis
- Cotrimoxazole (CPT)
No classical features to differentiate but TB IRIS

* Tender Hepatomegaly
* Preponderance of increase canaliculi enzyme
* Absence of jaundice
* Maintained synthetic liver function

IF THERE IS DOUBT SAFE TO MANAGE AS DILI
Management of DILI

Management during intensive phase

- Mild DILI
- Moderate DILI
- Severe DILI
**Mngt of Mild DILI**

**ALT/AST < 200IU/L or Total Bilirubin < 40μmol/L**

- Continue with TB treatment
- Continue with ART

- Repeat ALT/AST/Bilirubin in one week

- If normalized Stop Laboratory Monitoring

- If remains elevated but stable for 4 consecutive weeks consider other causes if worsen....
Mngt of Moderate DILI

ALT/AST > 200IU/L or Total Bilirubin irrespective 40μmol/L

- Stop Septrin
- Stop Anti TB, Stop ART:
  If the patient was on ART for > 6/12 Consider continuing the therapy
- Start Streptomycin/Ethambutol/Flouroquinolone later generation

*Streptomycin contraindicate if GFR < 60ml/min
Mngt of Moderate DILI: Isolated Jaundice

ALT/AST < 200IU/L or Total Bilirubin > 40μmol/L

- Continue with ART
- Stop Septrine if ALP and GGT are also elevated
- Stop RIF (RIF most likely)
- Ct with INH,PZA,EMB +Flouroquinolone
- Repeat Bilirubin after 7 days if does not normalize
  (?choledocholithiasis)
- Rechallenge after 2 – 3 weeks
Mngt of severe DILI

Clinically unwell; nausea, vomiting and abdominal pain

- Stop anti-TB, Septrin and ART
- Perform LFT, INR (PT and PTT)
  Blood Glucose (Hypoglycemia complicate LF)
- Start EMB/STREP/FLOUROQUINOLONE
  * GFR < 60ml/min
- Repeat ALT/AST/Bilirubin 2-3 day`
- Rechallenge if TB drugs ALT/AST < 100IU/L and Bilirubin ~
Rechallenge TB drugs (ALT/AST < 100 Normal Bilirubin)

- Day 1 RIF
- Day 3 Check ALAT/ASAT/Bilirubin
- Day 4 INH
- Day 7 Check ALAT/ASAT/Bilirubin
- Day 10 PZA
Conclusion

- Re-introduction of 1\textsuperscript{st} line drugs is preferred over the use of 2\textsuperscript{nd} line drugs.

- Rechallenge is not recommended for those with fulminant Hepatitis (Hepatic encephalopathy with coagulopathy).

- If DILI developed on NNRTI based regimen with EFV, rechallenge EFV in the case of mild DILI after the TB drug rechallenge incase or recurrent DILI, start a PI based regimen with LOP/r (with dose adjustment if receiving RIF).

- Cotrimoxazole should not be re challenged in HIV/TB patients.
Thank you for your attention