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

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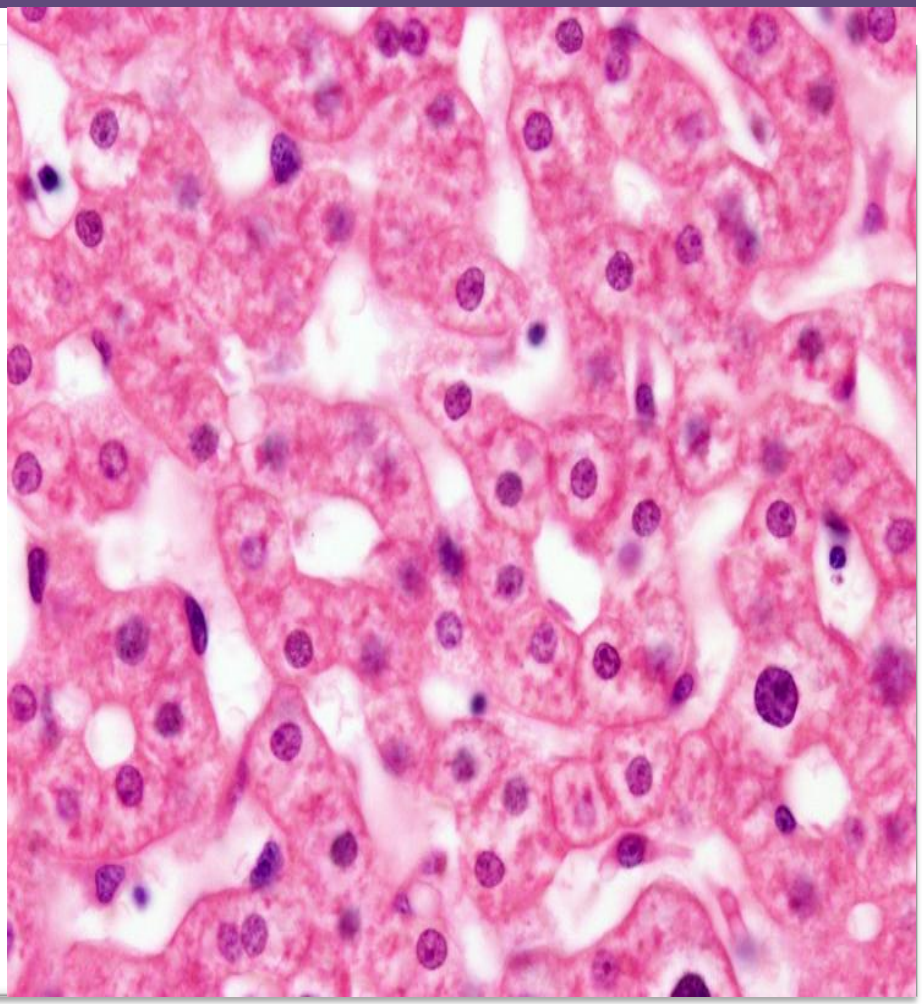
Presentation outline

① Definition of DILI

② Background

③ Mechanisms of DILI

④ Management of DILI



DILI diagnosis

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

OR

- ALT or AST > 200IU/L

OR

- Total serum bilirubin concentration > 40uml/L

Background

THE UNITED REPUBLIC OF TANZANIA

MINISTRY OF HEALTH AND SOCIAL WELFARE

THE NATIONAL TUBERCULOSIS AND LEPROSY PROGRAMME

MANUAL FOR MANAGEMENT OF TB AND LEPROSY IN TANZANIA

SIXTH EDITION
2013

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%

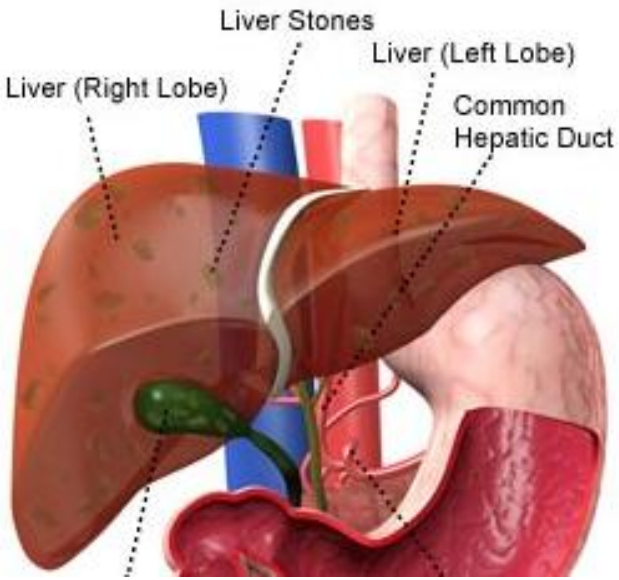
Antituberculosis drug-induced hepatotoxicity is uncommon in Tanzanian hospitalized pulmonary TB patients

Alma Tostmann[1,2], Jossy van den Boogaard[2,3], Hadija Semvua[4], Riziki Kisonga[5], Gibson S. Kibiki[4], Rob E. Aarnoutse[3] and Martin J. Boeree[1,2]

Background..

Drug Induced

- ❖ Primary compound
- ❖ Metabolite
- ❖ Immunological mediated response



Liver Injury

- ➢ Hepatocytes
- ➢ Biliary epithelial cells
- ➢ Liver vasculature

Background..

- 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 – impared drug metabolism

Differential diagnosis of DILI

ART may results 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)

DILI vs. TB IRIS

No classical features to differentiated 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 1st line drugs is preferred over the use of 2nd 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 re challenge 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