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Our Issues, Our Drugs, Our Patients

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Tuberculosis in renal and liver disease

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Mr HL – 56 year old man from Alex

- **Main complaint:**
  3 month history:
  marked loss of weight (20kg in 3mo.)
  Generalised abdominal pains
  Fever/ nightsweats

- **Background:** HPT, dyslipidemia
  newly diagnosed HIV: CD4 = 13
  Started on AZT/ 3TC/ EFV 2 weeks ago

- **Clinical examination**
  vitals – normal, generalised shotty nodes, bipedal oedema
  All other systems - normal
Investigations

FBC: WCC – 5.97/ Hb - 7.2/ Plt 316


Renal biopsy: necrotising granulomata

Urine: PCR – Mtb+ve, RIF/ INH sensitive
Tuberculosis in renal disease
TB in patients with renal disease

Epidemiology

- Increased incidence and prevalence of TB in ESRD and dialysis patients
- Increased rates of OIs especially TB in HIV-positive haemodialysis patients vs HIV-negative patients
- ?increased mortality

• Atypical clinical presentation:
  ▪ Pulmonary TB less common - <25%
  ▪ Disseminated forms predominate:
  ▪ Pleural effusions/ lymphadenopathy/ ascites/ hepatomegaly
  ▪ Tuberculous peritonitis in PD patients

• Often delayed diagnosis - with atypical presentation
Is TB treatment nephrotoxic?

**First line therapy:**
- INH/ Rif/ EMB – all nephrotoxic – RIF most commonly implicated in AKI (0.05%)
- Recovery rates around 90% by 120 days
- Common pathologies:
  a) acute interstitial nephritis
  b) acute tubular necrosis

**Second line therapy:**
- Aminoglycosides – daily vs 3 x/ week regimens?
  No difference in ototoxicity and nephrotoxicity

Chang CH, et al. BMC Infectious Diseases 2014;14(23):1471
• **Choice of drugs:** unchanged
  use standard drugs
  **EXCEPT**

  *With dose intervals*

• **Standard duration:**
  as per normal guidelines
Dosing adjustments in renal disease (BTS guideline)

• **Isoniazid**: full dose in all stages of renal failure (increase pyridoxine to 100mg to avoid risk of neuropathy) - not removed by dialysis

• **Rifampicin**: full dose in renal failure, not removed by dialysis

• Stage 4 (CrCl 15 – 30) and Stage 5 (CrCl <15) Chronic Kidney Disease – dosing intervals increased to 3x weekly for EMB/ PZA (In drug-resistant: aminoglycosides)

• **EMB**: mainly excreted in urine – increased ocular toxicity in renal failure

Milburn H, et al. Thoarx 2010;65:559-570
Tuberculosis in liver disease
TB in the setting of established liver disease

• Incidence of TB increased with chronic liver disease and liver cirrhosis

• Main challenge is decision regarding therapy – hepatotoxicity of first-line agents

• Risk of severe liver failure is markedly increased if hepatotoxicity develops in liver cirrhosis

• Clinical features similar to in renal failure – atypical presentations, increased dissemination/ extrapulmonary disease
Approach to starting TB therapy in patients with abnormal LFTs

• Confirm TB diagnosis

• Take extensive drug history – hepatotoxic HAART? TMP-SMX? Other chronic medication?

• Basic blood work up for raised liver enzymes
  - Blood count for bone marrow involvement
  - characterise pattern of liver dysfunction
  - viral hepatitis screen

• Abdominal u/s – looking for liver infiltration, splenic lesions, intra-abdominal nodes

• Consider IRIS

• Seldom: liver biopsy
Defining

Drug Induced Liver Injury

Table 2. DILI definition advocated in the SA setting

- ALT level >120 IU/l and symptomatic (nausea, vomiting, abdominal pain, jaundice); or
- ALT level >200 IU/l and asymptomatic; or
- Total serum bilirubin concentration >40 µmol/l
Hepatotoxic potential of first line TB regimen

- Risk factors: polymorphisms - slow acetylators,
- levels of drug, low baseline albumin, low BMI
- Age: >35 years old
- Men: higher incidence of DILI vs. Women: more severe DILI
- More disseminated disease – higher risk
- Underlying chronic Hepatitis B and C, other chronic liver disease
- HIV

Hepatic TB

- Clinically: hepatomegaly – 80%
  
  Ascites – 20%
  
  Jaundice – 20%

- If HIV+ - more likely to have pulmonary TB infection concurrently

- Bloods: commonly ALP/ GGT raised
  
  ALP: up to 750   
  GGT: up to 400
  
  occasionally: ALT/ AST raised up to 200

**Treatment**: standard anti-TB regimen
Which first-line drugs are implicated and how?

<table>
<thead>
<tr>
<th>Drug</th>
<th>hepatotoxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>transient enzyme increase is common, frank hepatitis in &lt;2%</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>dose related hepatotoxicity, variable picture: from reversible raised ALT/AST to frank hepatitis</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>raised enzymes common but frank hepatitis uncommon, isolated raised bilirubin – subsides with continued Rx</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>generally considered safe</td>
</tr>
</tbody>
</table>
What constitutes a “liver friendly” regimen?

• Ethambutol
• Aminoglycoside: streptomycin/amikacin/ kanamycin
• Fluoroquinolones: moxifloxacin

• SA HIV Clinicians Society Consensus statement: EMB/ Sm/ Mfx
• NICE Guidelines 2016: EMB/ Sm ± quinolone: Mfx/ Lfx
What about treating TB with other liver disorders in the mix?

- Calculate dose according to weight and avoid exceeding dose
- Consider a PZA-free regimen, means longer duration: PTB 9/12, EPTB 12/12
- Regular LFT checks: weekly initially then monthly
- Avoid alcohol – sounds simple but major predisposing factor
- Monitor closely for clinical deterioration, features of hepatitis – urgent bloods then stop Rx
Hepatotoxicity of drug-resistant regimens

- Not as common as standard TB Rx (about 16%)
- Mean time until onset >6 months
- One or more drugs stopped permanently in <2% of pts
- Rare to stop treatment entirely
- Doesn’t necessarily equate to poor prognosis

Hepatotoxicity of drug-resistant treatment – implicated agents

- Ethionamide – few%
- Quinolones – numerous case reports
- Para-aminosalicylic Acid (PAS) 0.5%
Re-introduction of TB treatment

• Many Different ways to skin a cat
• Durban, KZN: no difference in safety with re-introduction method (full rechallenge vs stepwise)
• Safe to monitor for recovery from DILI while holding treatment
• Johannesburg, GP: significant % will need modified regimens; ARVs & TB-DILI: longer, more severe DILI
• SA Guidelines: Start with full dose Rif, check LFTs, add full dose INH, check LFTs
Thank you