Managing TB with Pre-existing Liver and Kidney Disease

Alfred Lardizabal, MD
Global Tuberculosis Institute at UMDNJ

TB and Renal Disease

- 68 y/o male Samoan with end stage renal disease
- Multiple medical problems including CHF and DM
- Presented with 2 month history of progressively worsening cough
- No previous history of active TB or LTBI
- Chest x-ray obtained - abnormal

TB and Renal Disease

- Patient hospitalized
- Sputum smear AFB (+) x 3

TB and Renal Disease

- How would you treat this patient?
  1. Begin standard 4 drug treatment (RIPE) with no change in dose or frequency
  2. Avoid PZA and EMB, and treat with INH and RIF
  3. Use RIPE, but decrease the dosage of each drug
  4. Use RIPE, but increase the interval between doses for the PZA and EMB

Renal Insufficiency

- Treatment of TB in this setting is not uncommon because of the increased for progressing to active disease of ESRD patients
- In general, the doses of the anti-TB medications should not be reduced but rather the interval should be increased
**Renal Disease**

**TB Treatment Principles**

- For CrCl < 30 ml/min:
  - INH and Rif not affected and dose adjustments are not necessary (metabolized by the liver)
  - EMB, PZA and levofloxacin: maintain usual dose, but decrease frequency to 3x weekly
  - Give all drugs immediately after dialysis

- For CrCl > 30, but <70 ml/min:
  - Monitor closely for EMB optic neuropathy

**First-Line Agents & Hemodialysis**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Change frequency?</th>
<th>Removed by hemodialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>NO</td>
<td>+</td>
</tr>
<tr>
<td>Rifampin</td>
<td>NO</td>
<td>NO</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>YES</td>
<td>+</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>YES</td>
<td>+++</td>
</tr>
</tbody>
</table>

**TB and Renal Disease**

- Pt begins TB treatment with
  - INH 300 mg daily
  - Rifampin 600 mg daily
  - Ethambutol at 900 mg 3 X week after dialysis
  - PZA at 1500 mg 3 X week after dialysis
  - Vitamin B6 25 mg daily

- Nausea from uremia is difficult to distinguish from symptoms of drug induced hepatitis
- Are patients with ESRD at greater risk of adverse effects?

**TB and Renal Disease**

- After starting meds, pt states he has felt chronically nauseated but now feels worse since TB treatment started: “I’m dizzy and I think I need glasses”
  - Is this treatment related toxicity?
  - Are patients with ESRD at greater risk of adverse effects?
  - How would you evaluate and monitor this man?

**TB and Renal Disease**

- Pt is sent for ophthalmologic evaluation. Optic discs were normal and his visual acuity corrected to 20/20 with a new glasses prescription. LFT’s were unchanged

- Remember
  - ESRD patients are more frail and ill
  - Nausea from uremia is difficult to distinguish from symptoms of drug induced hepatitis
  - Close monitoring is mandatory

**Renal Disease**

- Resources:
  - TB Treatment Doses and Intervals in ESRD
**LTBI and Renal Disease**

- Prevention is the key!
- All patients with ESRD should have baseline TST or IGRA to assess for LTBI
- If LTBI present, must be very strongly encouraged to complete LTBI Rx
  - INH 300 mg daily or 900 mg twice or thrice weekly after dialysis for 9 months
  - Rifampin 600 mg daily or twice or thrice weekly for 4 months

**Isoniazid Toxicity in ESRD**

- One study observed pts on pyridoxine supplements <100 mg/day developed significant neurotoxicity
- Increased sensitivity of the dialysis population to INH neurotoxicity is predominantly due to:
  - Abnormal metabolism of pyridoxine resulting in low serum levels of the active metabolite, pyridoxal phosphate
  - There is rapid clearance of pyridoxal phosphate by hemodialysis, resulting in a severe deficiency of this active metabolite
- To prevent INH associated neurotoxicity, one retrospective study recommended giving 100 mg/day of pyridoxine supplements to hemodialysis patients requiring INH therapy
  - Nephron. 1993;64(2):303-6

**TB and Liver Disease**

- 55 y/o white male living in an “SRO” hotel who has been under care at the community clinic for alcoholic cirrhosis. Abstinence has been elusive.
- Today, he complains of fever, cough, weight loss and “just feels bad.” He has been drinking “a lot”
- You order a chest x-ray

**TB and Liver Disease**

- Sputum smears are AFB (+) x 3
- Blood chemistries are obtained:
  - Bilirubin = 3.6
  - Alkaline Phosphatase = 412
  - AST = 158, ALT = 112
  - INR = 1.8
  - Serum Albumin = 2.4

**TB and Liver Disease**

- What would you do now?
  1. Begin RIPE
  2. Hold treatment of TB until liver tests improve and he has dried out
  3. Begin INH, RIF, and EMB without PZA
  4. Begin Levo, EMB and Strep
  5. Begin RIF, EMB, and Strep +/- Levo
Liver sparing regimen
- Avoid all 3 drugs with potential liver toxicity, INH, Rif, and PZA
- Use the quinolone with the least incidence of hepatotoxicity, levofloxacin
- Use an injectable, usually streptomycin for its bactericidal activity

Patient was admitted and begun on EMB, Levo, and SM
- Developed DT’s on day 3 of hospitalization
- LFT’s initially rose with a peak Bili = 6.7 but then declined
- By day 18, Bili = 2.1, AST = 86, ALT = 56
- Patient clinically much better
- Rifampin 600 mg daily was begun

Would you have started Rifampin?
1. Yes, his liver is better and it will shorten his TB regimen
2. No, his liver is hanging on by a thread and it is not worth the risk

After beginning Rifampin, bilirubin rose to 12 and patient complained of nausea and complete loss of appetite
- Rifampin was stopped

What would you do now?
1. Try adding INH
2. Continue EMB, Levo, and SM
3. Add cycloserine to EMB, Levo, and SM

Cycloserine was added. The SM was stopped after 6 months and he completed 12 additional months of oral treatment
- (He also remained abstinent from alcohol)
Chronic Liver Disease & Liver Transplantation

- Chronic Liver Disease = 12th leading cause of death in the U.S.
- 90% survival 1st year post transplant; 5 year survival 70%
- 50% of death caused by infectious agents
- Over 95,000 transplants have been performed since 1988
- 5,316 transplants performed in 2009
- More than 15,000 people on the waiting list for a liver transplant

Source: United Network for Organ Sharing

TB incidence & Liver transplant

- Rates of TB disease in liver transplant recipients 1-6% in U.S. case series
- Case rate < 4/100,000, but 85/100,000 in liver transplant recipients
- Liver transplant recipients have an 18 fold increase in active TB

Outcome of TB in Liver Transplant Recipients

- Holty et al – systematic review examining survival in persons with TB after liver transplantation 1950-2007 in U.S.
- Findings
  - 7 studies; 139 active TB cases
  - 4 fold increase in case fatality rate
  - Short term mortality approx 31% overall; 36% if TB occurred within 5 months of transplant
  - Mortality higher with extensive resistance
- Mortality predictors
  - Absence of TB treatment (100%)
  - TB symptoms > 1 month
  - Treated with < 3 anti-TB medications

Holty et al, Liver Transpl, 2009

Adverse Drug Reactions: TB Treatment in Liver Transplant Recipients

- 30 (35%) had TB treatment stopped or changed due to adverse effects
- Of those 30:
  - 24 (73%) had hepatotoxicity
  - 9 (30%) had interference with immunosuppressive drug levels

Source: Holty et al., Liver Transpl 2009

Questions / Discussion