TB Medications and the Liver

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TB Medications

First Line
- Rifampicin
- Isoniazid
- Pyrazinamide
- Ethambutol
- Streptomycin

Second Line
- Quinolones
  - Moxi/Levofloxacin
- Injectables
  - Amikacin, Capreomycin
- Prothionamide
- PAS
- Cycloserine
- Linezolid
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- Macrolides
TB Medications which can cause liver injury

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Pathology

- Isoniazid: Hepatocellular steatosis and necrosis
- Rifampicin; Centrilobular necrosis +/- cholestasis
Mechanisms

- Not dose dependant
  - Overdose
- Not IgE mediated
  - allergy
- Idiosyncratic
- Probably toxic metabolites
‘Jaundice really ought to have wiped the smile off his face.’
Clinical features

- Non specific symptoms of liver injury
  - Jaundice
  - Nausea / vomit
  - Abdominal pain
  - Lethargy and malaise

- Differential
  - Viral hepatitis
  - Toxic eg alcohol
Laboratory diagnosis

- Raised transaminase
- Mild: ALT < 5 x ULN (<200)
- Moderate: ALT 5-10 x ULN (200 – 400)
- Severe: ALT > 10 x ULN (>400)
Incidence

Monotherapy (prophylaxis for LTBI)
- Isoniazid 0.5%
- Rifampicin 1-2%
- Pyrazinamide ?

Combination therapy (Active TB):
- Published range 2-27%
  - Varied settings and definitions
- Leeds 2006-2010 634 patients
  - ALT > 2 x ULN: 46 (7.3%)
  - ALT > 5 x ULN: 14 (2.2%)
Time of Onset

- Most common in 1\textsuperscript{st} 2 months
- Can occur any time in treatment

Leeds 2006-10

- Total: Mean 28/7 (range 3-306)
- Moderate-severe: Mean 42 days
- 12/14 within 56 days
Risk factors

- Increasing age
- Female
- Malnutrition
- Hepatitis B / C
- HIV
- Abnormal baseline liver enzymes
  (Leeds 2006-2010 – age only)
Case history (1)

- 72 year old female
- RA on infliximab
  - Negative mantoux pre treatment
- Pulmonary TB
- Standard treatment RHEZ
- Developed severe hepatits – progressed despite stopping drugs
- Died liver failure
38 year old Daughter of above
Contact screening
CXR Normal
Cough
Sputum AAFB smear pos
Commenced RHEZ
Within 2 weeks ALT > 5 x ULN
Stopped drugs
Subsequently culture identified as non-tuberculous mycobacterium
Genetic factors

- Polymorphisms in drug metabolism
- Slow acetylators
  - Isoniazid
- Other possible enzymes
- Currently not able to test / predict.
Adaptation

- In some cases, liver may adapt to drug
- After initial drug induced liver injury, may recover and then tolerate drug subsequently
Monitoring – NICE advice
*NICE CG117 2011*
Monitoring: BTS Advice
Joint Tuberculosis Committee Thorax 1998

- Pre-treatment LFT
- Inform patients of possible side effects
- Regular monitoring if pre-existent liver disease (weekly for 2 weeks, then 2 weekly for 2 months)
- Otherwise only repeat if symptoms
Monitoring: ATS Advice
Am J Respir Crit Care Med 2006

- Assessment of risk factors for hepatotoxicity
- Baseline history and examination including symptoms / signs of liver disease
- Screen for viral hepatits in those with risk factors
- Educate patient re potential side effects
Monitoring – ATS advice (continued)

LTBI

- Baseline blood tests not recommended unless risk factors
- Consider baseline and regular monitoring of ALT if >35 years
Monitoring – ATS advice
(continued)

Active TB

- Baseline ALT / Bilirubin / Alk Phos
- Routine monitoring of ALT if
  - Abnormal baseline
  - HIV / Hepatitis virus infection
  - Liver disease
  - Alcohol / other hepatotoxic drugs
  - ? Women
  - ? Older adults
Routine Monitoring

 Disadvantages:
  - Multiple blood tests
  - May result in discontinuing / interrupting treatment unnecessarily
  - Cost

 Benefits:
  - If routine, avoid missing high risk patient
  - May identify Liver injury at earlier stage
  - prevent serious complications
  - Cost cheaper than liver transplant
Leeds practice

- Baseline
- Repeat at 2/52, 4/52 and 8/52
- No further monitoring unless abnormal or symptoms
Abnormal baseline LFT

- Do NOT need to modify treatment regime
- DO monitor ALT
- In most cases, will IMPROVE on TB treatment
Management of hepatotoxicity–
NICE Advice

1.3.6.2 “If the patient’s liver function deteriorates significantly on drug treatment, advice on management options should be sought from clinicians with specialist experience of these circumstances.” [2006]
Management of Hepatotoxicity – BTS Advice

- ALT > 5x ULN: Stop drugs
- If not unwell or infectious – wait for ALT to return to normal
- If unwell / infectious – Streptomycin + Ethambutol +/- second line drug – preferably as in patient.
Management of Hepatotoxicity – BTS Advice (cont)

- Rechallenge in order;
  - INH – Rif – Pyrazinamide
- Isoniazid: 50mg – inc to 300 over 2-3 days
- Rifampicin: 75mg – 300 over 2-3 days – then 450/600mg over further 2-3 days
- Pyrazinamide 250mg – 1000 over 2-3 days – then 1.5g / 2g
- If further reaction, remove latest added drug.
BTS rechallenge regime

- Allows for possibility of adaptation
- Complicated drug increments
- Starting doses smaller than single tablet
- Daily monitoring – difficult if outpatient
Management of Hepatotoxicity – ATS Advice

- Stop drugs if:
  - ALT > 5 x ULN
  - ALT > 3 x ULN + jaundice or symptoms

- Check Hepatitis virus serology/other drugs / alcohol

- If indicated, until cause determined, treat with 3 drugs less likely to cause toxicity
Management of Hepatotoxicity—ATS advice (cont)

- When ALT < 2 x ULN –
- Start Rifampicin + Ethambutol
- After 3-7 days restart Isoniazid
- If symptoms recur or ALT increases again – stop last drug added.
- If necessary re-challenge with Pyrazinamide
- If tolerating Rifampicin and Isoniazid, and drug sensitive – continue without pyrazinamide (9/12 regimen)
Conclusion

- Consider risk factors, but most cases unpredictable
- Educate patients re potential side effects
- Check baseline ALT
- Baseline ALT high – standard regime
- Monitor if baseline ALT high or liver disease
- Consider routine monitoring 2/12
Conclusion - continued

- ALT < 5 x ULN – monitor
- ALT > 5 x ULN – stop drugs
- Investigate other causes
- If unwell / infectious – alternative drugs safer for liver
- When ALT normal – rechallenge sequentially
- Replan regime to take account of changes