An approach to

ANTI – TUBERCULAR DRUG INDUCED LIVER INJURY (DILI)

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Outline

- DILI – general concepts
  - Epidemiology
  - Mechanisms of DILI

- ATT- DILI
  - Incidence
  - Diagnosis
  - Risk factors and predictive scoring
  - Management with focus on rechallenge
  - Outcome of DILI
Drug-induced liver injury (DILI)

- Adverse drug reaction (ADR) - 3.6% of all admissions.
- 17% of all in-patients develop ADR with 0.5% mortality.
- An American study reports costs from 1,439 USD to 13,462 USD

- **DILI - Accounts for 7% of reported drug adverse effects**
  - Acute liver failure resulting in death or transplantation - 10%
  - Persistence of elevated liver enzymes > 6 months – 5-20%

- 19.1 cases per 100,000 inhabitants in Iceland in 2010-2011
  Gastroenterology 2013;144:1419-25

Consecutive patients with DILI from 1997 to 2008 from a tertiary care hospital in South India

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total on drug (% of total patients)</th>
<th>Total on drug who died (% of patients on drug)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-tuberculous drugs</td>
<td>181 (57.8%)</td>
<td>39 (21.5%)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>21 (6.7%)</td>
<td>1 (4.8%)</td>
</tr>
<tr>
<td>Dapsone</td>
<td>17 (5.4%)</td>
<td>2 (11.8%)</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>17 (5.4%)</td>
<td>-</td>
</tr>
<tr>
<td>Carbamazapine</td>
<td>9 (2.9%)</td>
<td>-</td>
</tr>
<tr>
<td>Cotrimaxazole</td>
<td>7 (2.2%)</td>
<td>-</td>
</tr>
<tr>
<td>NSAID: nemesulide (n=2), diclofenac (n=1), ibuprofen (n=2), celexocib (n=2), piroxicam (n=1)</td>
<td>8 (2.6%)</td>
<td>-</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>5 (1.6%)</td>
<td>-</td>
</tr>
</tbody>
</table>

Mechanisms of DILI

- **Type A, or intrinsic, adverse drug reactions**
  - Dose-related, predictable toxic effects of medications
    - Acute liver failure resulting from acetaminophen overdose

- **Type B or idiosyncratic adverse drug reactions**
  - Allergic, presenting with fever, rash, eosinophilia, and rapidly recurring on rechallenge
  - Non allergic
    - Not related to dose
    - Variable delay or latency period
    - Associated with drug, patient, and environmental risk factors
    - Difficult to predict.

Mechanisms of DILI

- Transformation (Phase 1)
- Conjugation (Phase 2)
- Transport into bile canaliculus (Phase 3)
Pattern of liver injury

- \( R = \frac{\text{ALT/ULN}}{\text{ALP/ULN}} \)

Hepatocellular pattern  \( R \geq 5 \)  Mixed pattern  \( R > 2 \) and \( < 5 \)
Cholestatic pattern  \( R \leq 2 \)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phenotype</th>
<th>Histological features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen</td>
<td>Acute hepatic necrosis</td>
<td>Collapse and centrolobular necrosis</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Cholestatic hepatitis</td>
<td>Ballooned hepatocytes with inflammation</td>
</tr>
<tr>
<td></td>
<td>Immunoallergic hepatitis</td>
<td>Eosinophilic infiltration</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>Acute viral hepatitis like</td>
<td>Inflammatory infiltrates</td>
</tr>
<tr>
<td>Valproate</td>
<td>Acute fatty liver with lactic acidosis</td>
<td>Hepatic steatosis</td>
</tr>
<tr>
<td>Methotrexate</td>
<td>Cirrhosis</td>
<td>Fibrosis without inflammation</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Granulomatous hepatitis</td>
</tr>
</tbody>
</table>
Factors which influence susceptibility to DILI

Host

Age
Sex
Weight
Genetic polymorphisms

Drug

Lipophilicity
Dose
Duration
Metabolism

Environment

Alcohol
Diet
Tobacco
Causality assessment

- No specific tests to confirm the diagnosis of DILI

- **Clinical notes for causality assessment**
  - A temporal relationship with respect to medication exposure
  - Time of DILI onset - time of the first qualifying laboratory tests/clinical symptom
  - Course of the reaction - fall by at least 50% from the peak value
  - Presence of risk factors
  - The dose (defined daily dose or cumulative dose) of a drug may be important

- Roussel Uclaf Causality Assessment Method (RUCAM), Maria and Victorino clinical diagnostic scale

Tuberculosis in India

- TB remains a major global health problem
  - India - 25% of world’s total TB cases in 2015.
  - India, China and Russia - 45% of the combined total of 580000 MDR TB patients.

Adverse reactions mainly DILI

↓

Poor adherence to treatment

↓

Treatment failure and emergence of drug resistant tuberculosis.

- Reasons for default from treatment – 43% due to adverse events
  
Incidence of anti tubercular DILI

- **Indian studies**
  - 10.5% - Deepak et al. *J Gastroenterol Hepatol.* 2005
  - 9.48% - Saha et al. *J Prim Care Community Health.* 2016
  - 9.7 % (95% C.I 7-13.2%) – Prospective study of 393 patients from CMC (2013-14)

- **Western studies** – a meta analysis of 14 studies show an incidence of 4.38 %

- **Reasons for difference**
  - Ethnicity, malnutrition, more advanced disease at diagnosis
  - Non exclusion of Acute viral hepatitis

Definition of ATT DILI

- Normalization of liver enzymes and resolution of signs and symptoms of hepatotoxicity after withdrawal of all anti-TB drugs

- Presence of at least one of the following:
  - > 5 times normal of AST/ALT
  - > 3 times normal of AST and/or ALT or > 2 times normal of total bilirubin together with anorexia, nausea, vomiting, and jaundice.

- Exclusion of acute viral hepatitis (A,B and E).

Case 1

- Mrs. S is admitted and diagnosed to have sputum positive pulmonary tuberculosis. She was started on weight based first line anti-tubercular drugs.
- Baseline LFT was normal.
- She was well and planned for discharge.
- LFT repeated before discharge
  - 1.3/0.9/6.5/3.5/120/110/145

- What is your management plan?
Concept of hepatic adaptation

- Physiological adaptive responses to certain drugs
  - Induction of survival genes (anti-oxidant, anti-inflammatory and anti-apoptotic)
  - Hepatocyte proliferation
  - Metabolic enzyme induction

- May reflect slight, non-progressive injury to hepatocyte mitochondria and membranes
- Rarely leads to inflammation, cell death or significant histological changes
- Liver function tests normalizes despite continuation with treatment

- Lack of awareness of this entity leads to unnecessary interruption of treatment

- Isoniazid, is a classical example
Management of case 1

- This patient was asymptomatic and liver enzymes less than 5 times ULN
- Hence first line ATT was continued and serial LFT done showed 1/0.6/7/3.5/45/32/108
- Completed 6 months ATT and well.

**Asymptomatic mild elevation** of liver enzymes – No need to stop hepatotoxic drugs

**HEPATIC ADAPTATION not DILI**
Case 2

- 37 years old gentleman Mr. V was recently admitted and diagnosed to have HIV infection clinical stage 4 and disseminated tuberculosis.
- He was started on daily weight based anti-tubercular drugs (ATT)
- Baseline LFT showed 1.2/0.8/6/2.8/42/24/128

- 12 days after initiation of ATT,
  - he presented to the casualty with 3 days history of yellowish discoloration of eyes and urine associated with right upper quadrant abdominal pain.

- On examination, he was conscious, oriented and afebrile.
- Pulse rate 108/min, BP 120/70 mm of Hg, RR 16/minute
- He was icteric
- Systemic examination – hepatomegaly 3 cm non tender otherwise normal
Investigations

- Hb 10.8 g/dl TC – 4800 cells/cu.mm Platelet 1.5 lakh cells/cu.mm
- DC 70% Neutrophils and 30% lymphocytes
- Creatinine 0.8 mg/dl

- LFT – 5.4/5.1/6.2/2.8/1509/548/623
- Acute viral hepatitis screen( A/B/E) negative

- What is your diagnosis ?
- What is your management plan ?
Case 2

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- Icteric and systemic examination – hepatomegaly 3 cm non tender.
Risk factors for ATT DILI

- Age > 35 years
- Female gender
- Cavitory disease, multibacillary TB and disseminated
- Daily regimen
- Malnutrition
- Chronic liver disease
- Genetic polymorphisms like N-acetyltransferase 2 (NAT2), CYP 2E1 and glutathione S-transferase

Independent risk factors for DILI
- data from our centre

- HIV infection (OR 2.84, p value 0.002, 95% C.I 1.42 – 5.67)
- Daily regimen (OR 4.46, p value 0.003, 95% C.I 1.55 – 12.81)
- Disseminated disease (OR 1.769, p value 0.006, 95% C.I 1.23-2.55)
- Hypoalbuminemia (OR 1.92, p value 0.045, 95% C.I 1.01 – 3.68)
- Chronic liver disease (OR 4.72, p value 0.004, 95% C.I 1.5-14.82)
Predictive scoring system – data from our centre

<table>
<thead>
<tr>
<th>Risk factors for DILI</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>HIV infection</td>
<td>3</td>
</tr>
<tr>
<td>Chronic liver disease</td>
<td>4</td>
</tr>
<tr>
<td>Daily treatment Regimen</td>
<td>2</td>
</tr>
<tr>
<td>Female gender</td>
<td>2</td>
</tr>
<tr>
<td>Hypoalbuminemia (S.albumin &lt; 3.5 g/dl)</td>
<td>2</td>
</tr>
<tr>
<td>Disseminated disease</td>
<td>2</td>
</tr>
</tbody>
</table>

Total Score of $\geq 5$ predicts DILI with sensitivity of 74% and specificity of 67%
Proposed Clinical rule for prediction of DILI
(based on scoring system)

_Situations of high risk of DILI_

- **Chronic liver disease + any one risk factor**
  (low albumin or HIV infection or disseminated disease or female gender).

- **HIV + any one risk factor**
  (low albumin or chronic liver disease or disseminated disease or female gender)

- **Low albumin+ Disseminated disease+ female gender**
  (In patients who are HIV negative and no chronic liver disease)

In all above mentioned situations, **careful monitoring** advised.
Guidelines for monitoring LFT

- All patients should be educated about the disease, adverse events
  - To report immediately if symptoms arise

- Routine measurement of baseline LFT not recommended in the absence of clinical risk factors by WHO or national guidelines

- In the presence of clinical risk factors / other hepatotoxic medications - baseline LFT recommended.

- Serial Total bilirubin / ALT in the presence of risk factors/liver disease.
  - 2 weeks followed by two weekly till normal

- Once normal, further repeat tests are only required for symptoms.
Monitoring symptoms and LFT at regular intervals in the initial month essential in patients with risk factors

<table>
<thead>
<tr>
<th>Outcome measures and reintroduction</th>
<th>Group A (n = 21)</th>
<th>Group B (n = 24)</th>
<th>P or Z values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latency period, days (range)</td>
<td>12.6 ± 3.6 (7–30)</td>
<td>29.8 ± 5.3 (7–65)</td>
<td>S</td>
</tr>
<tr>
<td>Symptomatic period before detection of toxicity (range)</td>
<td>2.3 ± 0.7 (1–6)</td>
<td>11.5 ± 1.2 (7–15)</td>
<td>S</td>
</tr>
<tr>
<td>Requirement of hospitalization</td>
<td>0 (0%)</td>
<td>10 (41.6%)</td>
<td>S</td>
</tr>
<tr>
<td>Requirement of ICU</td>
<td>0 (0%)</td>
<td>7 (29.1%)</td>
<td>S</td>
</tr>
<tr>
<td>Mortality</td>
<td>0 (0%)</td>
<td>4 (16.6%)</td>
<td>S</td>
</tr>
<tr>
<td>Normalization of LFT</td>
<td>21 (100%)</td>
<td>20 (83.3%)</td>
<td>NS</td>
</tr>
<tr>
<td>Time for normalization of LFT after ATT withholding (range)</td>
<td>20.2 ± 6.2 (7–40)</td>
<td>24.8 ± 5.4 (10–78)</td>
<td>NS</td>
</tr>
<tr>
<td>Reintroduction attempted</td>
<td>21 (100%)</td>
<td>18 (90%)</td>
<td>NS</td>
</tr>
<tr>
<td>Successful reintroduction</td>
<td>20 (95.2%)</td>
<td>18 (100%)</td>
<td>NS</td>
</tr>
</tbody>
</table>

ATT; antituberculosis therapy; ICU, Intensive Care Unit; LFT; liver function tests; NS, not significant; S, significant.

- Group A – Patients with DILI who were periodically followed up
- Group B – patients who are treated elsewhere and presented with DILI

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Onset and normalization of LFT - data from our centre

10, 23%
20, 47%
13, 30%

Mean time duration for normalization of LFT 22 ± 14 days
Case 2

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Onset and normalization of LFT - data from our centre

10, 23%
20, 47%
13, 30%

Mean time duration for normalization of LFT  22 ± 14 days
Further management – case 2

- First line hepatotoxic drugs were withheld (INH, RIF, PYZ)
- Started on Amikacin, Levofloxacin and ethambutol
Principles of management of DILI

- All hepatotoxic drugs stopped, and changed to non-hepatotoxic regimen (Amikacin, fluoroquinolone and ethambutol)

- Rechallenge of a drug considered if its potential benefit > risks.

- In case of prolonged or severe hepatotoxicity, rechallenge with pyrazinamide may be avoided.

- During rechallenge, if the patient develops hepatotoxicity, the last drug added will be omitted.

- Treatment duration extended if any of the first line drugs omitted.
  - ± addition of other drugs like fluoroquinolones/aminoglycosides

Case 2 - continued

- LFT normalized within 2 weeks.

- Restarted on rifampicin 150 mg on day 1, with monitoring of LFT escalated to 600 mg per day.

- Later Isoniazid 150 mg once daily and 3 days later, patient presented with clinical features of hepatitis.

- LFT done showed 6.1/5.2/6.2/2.1/258/262/301.
Case 2 - continued

- Impression: Rechallenge hepatitis with Isoniazid
- Isoniazid and pyrazinamide was not rechallenged further.
- Patient treated with modified ATT regimen for a total of 1 year.
Various guidelines for rechallenge

<table>
<thead>
<tr>
<th>Authority</th>
<th>Rechallenge</th>
<th>Recommended LFT monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Thoracic society</td>
<td>RIF full dose then After 3-7 d INH full dose PYZ only if mild DILI</td>
<td>Check ALT every 3-7 days</td>
</tr>
<tr>
<td>British thoracic society</td>
<td>INH $\rightarrow$ RIF $\rightarrow$ PYZ Dose escalated every 2-3 days</td>
<td>Daily monitoring of LFT</td>
</tr>
<tr>
<td>ERS, WHO, IUATLD</td>
<td>Start all drugs at full dose</td>
<td>LFT monitoring</td>
</tr>
</tbody>
</table>
Rechallenge following DILI

- A prospective study from AIIMS Delhi and SVIMS, Tirupathi
  - A total of 175 patients with a diagnosis of ATT DILI were randomized to receive 1 of 3 arms [All 3 drugs at same time Vs ATS vs BTS]

  **No significant difference between 3 arms**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Arm I (n = 58)</th>
<th>Arm II (n = 59)</th>
<th>Arm III (n = 58)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maximum bilirubin level, mg/dL</td>
<td>0.94 ± 0.64</td>
<td>0.86 ± 0.45</td>
<td>0.82 ± 0.46</td>
<td>.59</td>
</tr>
<tr>
<td>Maximum AST level, IU/L</td>
<td>71.5 ± 58.0</td>
<td>64.7 ± 69.3</td>
<td>63.6 ± 62.7</td>
<td>.84</td>
</tr>
<tr>
<td>Maximum ALT level, IU/L</td>
<td>72.8 ± 79.7</td>
<td>68.2 ± 58.3</td>
<td>60.8 ± 62.1</td>
<td>.73</td>
</tr>
<tr>
<td>No. (%) of patients with recurrence of DIH after reintroduction of anti-TB drugs</td>
<td>8 (13.8)</td>
<td>6 (10.2)</td>
<td>5 (8.6)</td>
<td>.69</td>
</tr>
<tr>
<td>Time period from reintroduction of anti-TB drugs to recurrence of DIH, median days (range)</td>
<td>14 (5–28)</td>
<td>21 (14–28)</td>
<td>21 (14–35)</td>
<td>.69</td>
</tr>
</tbody>
</table>

Outcome of DILI in our study

- 36 patients had complete resolution (84%)
- 4 of them needed ICU care.
- 4 of them had features of acute hepatic failure.
- All cause mortality - 4.7% (2 patients)

<table>
<thead>
<tr>
<th></th>
<th>Rechallenge hepatitis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Isoniazid</td>
</tr>
<tr>
<td><strong>ATS guidelines</strong></td>
<td>2 out of 16 (12.5%)</td>
</tr>
<tr>
<td><strong>BTS guidelines</strong></td>
<td>2 out of 11 (18.2%)</td>
</tr>
</tbody>
</table>
Examples of rechallenge following DILI
Example 1

Presence of one or more risk factors for development of DILI
Severe icteric hepatitis

- INH/ RIF
- Would advise rechallenge at escalating doses
- Pyrazinamide rechallenge may be avoided
Example 2

Mild icteric hepatitis
No clinical risk factors

- Would advise rechallenge with all 3 drugs at the same time
Example 3

- Mild icteric hepatitis
- With clinical risk factors

- INH $\rightarrow$ RIF $\rightarrow$ PYZ at full dose at a time
Example 4

- Cholestatic picture with/without risk factors
  
  - **Option 1**: May discontinue only RIF and continue the rest
  
  - **Option 2**: if severe → stop all 3 drugs and *avoid RIF rechallenge* and so modified ATT for extended duration
Take home messages

- Every physician should be aware of ATT DILI.
- Assess for risk factors before initiation of ATT and importance of patient education.
- Baseline LFT for patient with risk factors and careful monitoring of those patients.
- Distinguishing hepatic adaptation from DILI.
- Follow the rules of rechallenge based on pattern and severity of liver injury.
- Better to be careful in rechallenge to prevent rechallenge hepatitis.
- In case of modified ATT → treatment duration extended.
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