Is chronic liver disease after acute hepatocellular DILI over-estimated? (20 min)

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Types of chronic injury

- Vanishing bile duct syndrome
- Drug-induced (auto) immune hepatitis
- Cirrhosis-methotrexate prototype
Case reports on the development of cirrhosis following DILI

- Chronic liver disease from drugs: Einar Björnsson, Kaplowitz book
  - Isoniazid
  - Methyl-dopa
  - Valproat
  - Enalapril
  - Amiodarone
  - Ebrotidine
DILI and chronic liver injury

• Aithal G, Day C. The natural history of histologically proved DILI. Gut 1999;44: 731

• Patients identified in a histological database

• A total of 13/33 (39%) had chronic abnormalities in liver tests and/or on imaging a few years after DILI (median follow-up 5 years)

- 28/493 (5.7%) had persistent abnormalities
- Most frequent causes: Augmentin, bentazepam, atorvastatin, captopril
- Cholestatic patterns of DILI were significantly more prone to chronicity than the hepatocellular type
DILI and chronic liver injury

• Bjornsson et al. Aliment Pharmacol Therap 2007;26: 79-85. found abnormalities in 3/50 (6%) of patients without a known liver disease at follow-up

• Two patients were taking the same drug! (diclofenac and nitrofurantoin) that had been identified earlier as the cause of DILI
DILI and chronic liver injury

• Unclear whether these biochemical and/or histological abnormalities will lead to liver related morbidity and mortality in the long-run
• Overall 784 DILI cases with concomitant jaundice reported to the Swedish authorities, 72 died (9.2%)

• Validated the Hys rule

- 685 patients with jaundice due to DILI were linked with the Swedish Hospital discharge registry

- 23 (3.4%) had been hospitalized for liver disease after a mean follow up of 10 years and 5 had liver-related mortality

- 8 developed cirrhosis (7 decompensated, 5 died)
- 5 with cryptogenic cirrhosis where the DILI might have played a role
- Thus, among the 23 patients, 5 had a liver related death.
Clinical and biochemical parameters

<table>
<thead>
<tr>
<th>Subject</th>
<th>Drug</th>
<th>Follow-up (years)</th>
<th>Duration of treatment (days)</th>
<th>Bilirubin ULN</th>
<th>New liver diagnoses during Follow-up</th>
<th>Abnormal liver tests at follow-up</th>
<th>Liver-related mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>M58</td>
<td>Amoxicillin</td>
<td>3</td>
<td>26</td>
<td>3.8 (CS)</td>
<td>Yes, cryptogenic cirrhosis</td>
<td>Yes</td>
<td>Complications of cirrhosis</td>
</tr>
<tr>
<td>F59</td>
<td>Ranitidin</td>
<td>8</td>
<td>90</td>
<td>7 (HC)</td>
<td>Yes AIH + ALD</td>
<td>Yes</td>
<td>Complications of cirrhosis</td>
</tr>
<tr>
<td>M34</td>
<td>Fluconazol</td>
<td>4</td>
<td>21</td>
<td>13.8 (CS)</td>
<td>No, known ALD prior to DILI</td>
<td>Yes</td>
<td>Complications of cirrhosis</td>
</tr>
<tr>
<td>F84</td>
<td>Hydro-chlortiazide/Amilorid</td>
<td>3</td>
<td>380</td>
<td>15 (HC)</td>
<td>Yes, cryptogenic cirrhosis</td>
<td>Yes</td>
<td>Complications of cirrhosis</td>
</tr>
<tr>
<td>F51</td>
<td>Fluoxetine</td>
<td>4</td>
<td>28</td>
<td>8.2 (HC)</td>
<td>No, known ALD prior to DILI</td>
<td>Yes</td>
<td>Complications of cirrhosis</td>
</tr>
<tr>
<td>F71</td>
<td>Multiple</td>
<td>4</td>
<td>365</td>
<td>3.3 (CS)</td>
<td>Yes (another DILI)*</td>
<td>Yes</td>
<td>Not liver-related mortality</td>
</tr>
<tr>
<td>F31</td>
<td>Halothane</td>
<td>11</td>
<td>1</td>
<td>4.5 (HC)</td>
<td>No</td>
<td>Yes</td>
<td>Stroke</td>
</tr>
</tbody>
</table>

*Not liver-related mortality

*Suicide

*Complications of cirrhosis

*Not liver-related mortality

- Duration of therapy before DILI was longer in patients with liver related morbidity and mortality (135 vs. 53 days; p<0.0001)
- Those who had a protracted reaction were 6/7 with chloastatic pattern. However, 6 patients followed for a mean of 13 years, only one still had abnormal liver tests
Conclusions

• Development of clinically important liver disease after severe DILI associated with jaundice is rare after acute DILI.

• However decompensated “cryptogenic” cirrhosis developed in some patients with fatal outcome in which DILI might have played a role in this development.
Idiosyncratic Drug-Induced Liver Injury Is Associated With Substantial Morbidity and Mortality Within 6 Months From Onset
Fontana et al. Gastroenterology 2014

• Overall 113/598 (18.9%) met at least 1 of the 6 protocol-defined criteria for chronic DILI.

• Chronic DILI were significantly more likely to be African American (18.6% vs 8.7%; \( P < .01 \)), have malignancy and receive ant-neoplastic drugs.
Chronic vs. acute DILI

• Median duration of medication use was also significantly longer in those that developed chronic DILI compared with those who did not (51 vs 30 days; \( P < .01 \)).

• The presenting serum ALP, African-American race, active malignancy, and heart disease, were independent predictors of chronic DILI.
Conclusions: Chronic vs. acute DILI

• Chronic liver injury developed in 18.9% but was generally mild at 6 months of follow-up, and ”long-term outcomes will require additional study”.

• No decompensation was reported.

- Out of 298 patients enrolled 273 (92%) resolved 61 year from DILI recognition and 25 patients (8%) were chronic.

- Independent risk factors for chronicity were older age [OR: 1.06, p = 0.011], dyslipidemia [OR: 4.26, p = 0.04] and severe DILI [OR: 14.22, p = 0.005].
Screened population 850

Met inclusion criteria 351

Study cohort 298

Inclusion criteria:
- Survival of the index episode without a liver transplantation
- DILI cases that resolved or DILI cases that did not resolve but had follow-up ≥1 year
- During follow-up all cases had appointments scheduled at least every 6 months in the first year and at least annually in the consecutive years.

Exclusion criteria:
- Underlying chronic liver disease (22)
- Systemic diseases affecting the liver (17)
- Miscellaneous causes (14)

Chronic (≥1 year) 25 (8%)

Up to 3 years

Non classifiable, Loss of follow-up after 1 year 8 (32%)

Resolution 16 (64%)

No resolution 12 (75%)

After 3 years

Resolution 4 (25%)

No resolution 12 (75%)

Acute (≤1 year) 273 (92%)

≤3 months HC ≤3 months Chol-mix 174 (64%)

>3 months HC >6 months Chol-mix 99 (36%)
Definition and risk factors for chronicity following acute idiosyncratic drug-induced liver injury

- Chronicity: Persistent ALT, AST, TB or ALP elevations >1 xULN or imaging or histology data compatible with chronicity (irrespective of laboratory data) after one year from DILI recognition. Patients whose liver enzyme values returned to within laboratory references
Drug class and histology

- Main drug classes involved in chronicity were statins (24%) and anti-infectives (24%).
- Histological examination in chronic patients demonstrated two cases with ductal lesion and seven with cirrhosis.
- No decompenstation was reported
Discussion

• "Aside from a small number of cases of early onset cirrhosis which becomes quiescent, gradual resolution at 1 or 3+ years or persistence of borderline laboratory abnormalities beyond 3 years is seen in a very small percentage of cases. The persistence of these very mild abnormalities is of uncertain significance but does not appear to be an important clinical problem. Hence, the term “chronic” is somewhat controversial as there are “chronic DILI patients” who eventually resolve the liver damage".
Conclusions

• One year (92% resolved within one year) is the best cut-off point to define chronic DILI or prolonged recovery, with risk factors being older age, dyslipidemia and severity of the acute episode.

• Statins are distinctly related to chronicity. ALP and TB values in the second month could help predict chronicity or very prolonged recovery.
Yes chronic liver disease after acute HC DILI is overstimated!

- During long-term follow-up most people normalize their liver tests
- Decompensation has anecdotally been reported
- Evidence for clinically significant liver related morbidity due to chronic DILI is weak
The liver is a forgiving organ