DRUG-INDUCED LIVER INJURY

How the clinical signature impacts benefits & risks

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The views being presented are my own and not an official position of the FDA
Overview of Presentation

• DILI risk assessment in benefits & risk analysis
  • Key elements
  • Temporal variables
• Acute DILI vs benefits: timeline graph profiles
• Examples of distinct agent-specific DILI forms
  • immunoallergic, ‘classic’ & autoimmune
• RUCAM criteria in the face of different DILI clinical & temporal signatures
Benefits vs Risks

A simplified framework

**BENEFITS**

**RISKS**

**Treatment Indicated for Life-threatening / debilitating disease**

- High clinical response rates with improved long-term survival
- Rapid & sustained clinical response
- Unremarkable SAE risk profile
- Lack of equivalent alternative treatments

**Treatment Indicated for Minor symptomatic non-debilitating condition**

- Low clinical response rates with no improvement of long-term survival
- Delayed or transient clinical response
- Substantial SAE risk profile; Difficult to mitigate risk
- Safe & effective alternative treatments

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Assessment of DILI Risk

Key Components

• Risk Components
  • Population frequency
  • Drug-associated Causality
  • Clinical Severity
  • Clinical Signature Temporal Features

• Risk factors
  • Genomic
  • DDIs
## Levels of DILI Severity

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>Death/Tx</td>
</tr>
<tr>
<td>4</td>
<td>Acute Liver Failure</td>
</tr>
<tr>
<td>3</td>
<td>Serious: Disabled, Hospitalized</td>
</tr>
<tr>
<td>2</td>
<td>Hy’s Case: Detectable Slight Functional Loss</td>
</tr>
<tr>
<td>1</td>
<td>Serum Enzyme Elevations Only; Many People Adapt</td>
</tr>
<tr>
<td>0</td>
<td>Most People Tolerate Exposure - No Adverse Effects Seen</td>
</tr>
</tbody>
</table>
Categories of DILI Likelihood

5  **definite**, almost certain (estimated range >95%)
4  **very likely** (estimated range >75 to 95%)
3  **probable** (estimated range >50 to 75%)
2  **possible** (estimated range >25 to 50%)
1  **unlikely** (estimated range 5 to 25%)
0  **very unlikely** (estimated range <5%)

percentage ranges do not imply exactness, but may be helpful as adjectives to get more consistency between evaluators

*FDA categories consistent with NIH DILIN scale, but inverted*
Assessment of DILI Risk

Temporal Features

- Time to onset of DILI
- Time to Peak of Liver damage
- Duration & Profile of Liver Dysfunction
- Time to resolution
Offset of Benefits vs DILI Risk

Temporal features of treatment to consider

**Biopharmaceutical Lens**
Duration of treatment / Cumulative Exposure

- Response times of biosystem therapeutic targets
- Profiles of liver cell cytoprotective & regenerative responses
- Profiles of drug & metabolite levels in liver cells
- Profiles of drug-induced adaptive & innate immune activities
- Profiles of drug-related autoimmunity
Offset of Benefits vs DILI Risk

Temporal features of treatment to consider

**Clinical Lens**

Duration of treatment / Cumulative Exposure

- Time to attain benefit
- Permanence vs transience of benefit

**Offset**

- Time to onset of increasing DILI risk
- Permanence vs transience of DILI risk
- Acute vs chronic forms of DILI risk
Drug A: Benefits vs DILI Risk

Time-line profile in treatment population

% with Life-Saving Benefits*
% with Life-Threatening DILI*

**Scales are for hypothetical discussion & have no regulatory inference**
Drug A: Benefits vs DILI Risk

Time-line profile in treatment population

---

Treatment

% with Life-Saving Benefits

% with Life-Threatening DILI

Treatment Time

**Scales are for hypothetical discussion & have no regulatory inference**

Day 1  Day 3  Day 4  Day 15  Day 30  3 Mo  3 Yr

Benefits-DILI Risk

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Drug B: Benefits vs DILI Risk

Time-line profile in treatment population

**Scales are for hypothetical discussion & have no regulatory inference**
Drug C: Benefits vs DILI Risk

Time-line profile in treatment population

Treatment Time

**Scales are for hypothetical discussion & have no regulatory inference**

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Drug D: Benefits vs DILI Risk

Timeline profile in treatment population

Clinically Important Benefits (%)

% with Life-Threatening DILI

**Scales are for hypothetical discussion & have no regulatory inference**

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Diverse DILI Phenotypes/Clinical Patterns

• Acute hepatic necrosis
• Acute viral-like hepatitis
• Immunoallergic hepatitis
• Drug-associated autoimmune hepatitis
• ALF
• Cholestatic hepatitis
• Bland cholestasis
• Persistent Hepatitis
• Acute fatty liver & lactic acidosis
• NASH
• Sinusoidal obstruction syndrome
• Chronic hepatitis
• Vanishing bile duct syndrome
• Nodular regeneration
• Cirrhosis

*DILIN; [Fontana et al.; Hepatology, 52, 2010]*
Selected Idiosyncratic DILI Signatures

Temporal risk profiles

- Immunoallergic hepatitis
- Acute viral-like hepatitis (‘Classic’ type)
- Drug-associated autoimmune hepatitis phenotypes
Drugs Associated with Immunoallergic DILI

Examples

- Antibiotics
  - sulfa drugs
  - quinolones
  - ketolides
- Aromatic anticonvulsants
- Allopurinol
- Celecoxib
- Nevarapine
- Efavirenz
Immunoallergic Clinical Signature

telithromycin-associated DILI

- First oral ketolide approved for treatment of CABP, AECB & bacterial sinusitis
- Hepatotoxic profile characterized in a comprehensive review of P-M published and spontaneously reported cases
  - 42 cases evaluated by FDA expert panel
    - Serious outcomes: 32/42 hospitalized; 4/42 died; 1/42 liver x-plant
    - 25/42 developed hepatocellular jaundice
    - 26/42 assessed as ‘probable’ or ‘highly likely’
    - 4/42 had previous telithromycin exposure
    - Clinical signature marked by very short time to onset (median 10 days, range 2-43 days), rapid onset of fever (29%), abdominal pain (45%) and jaundice. Some cases reported eosinophilia (19%) and/or ascites (17%)
      - Immunoallergic features suggest new or previous hypersensitivity to telithromycin or a metabolite, or cross-sensitization with a structurally-related macrolide
‘Classic’ Idiosyncratic Clinical Signature

**Ximelagatran-associated DILI**

- Prodrug of melagatran (a direct thrombin inhibitor)
- Not approved in US & withdrawn elsewhere because of hepatotoxicity
- Long-term exposure (LTE) protocols for 2ndary prevention of VTE & thromboembolism associated with non-valvular Afib
- Cases of *advanced* liver injury marked by concurrent increases of serum ALT >3x ULN & total bilirubin >2x ULN
- 0.5% ximelagatran LTE groups (n=37/6,948) developed *advanced* liver injury with 1 related death vs 0.08% (n=5/6,230) in comparator groups
- ALT > 3x ULN: 7.6% ximelagatran LTE subjects (n=531/6,948) vs 1.1% warfarin LTE subjects
- High rates of adaptation with continued treatment
- ALT > 3x ULN: Time to onset typically ranged between 2 weeks and 6 months of treatment (93% of cases); Highest incidence 2-3 months; 30% of cases occurred after 3 months; 7% after 6 months; 2% after 12 months
SPORTIF V eDISH Plot: Peak Liver Tests*

Ximelagatran (X) vs Warfarin (C)

‘Classic’ Idiosyncratic DILI

Ximelagatran-associated DILI (SPORTIF V); Case 1

Drug-induced Autoimmune Injury

Hapten Hypothesis

Initiators

Haptens
Drug Metabolites

Second Stress Signals:
Inflammatory, Cellular, or Environmental

Drivers

Changes in Lymphocyte Genetic/Epigenetic Controls
Enhancement of Auto-reactive Cytotoxic T/NK/B Cell Activities
Alteration of Immune Regulatory T Cells
Breaking of Self-tolerance
Unmasking of Underlying Immune Disease

Danger Hypothesis

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Drug-induced AIH & IMH Signatures

• Acute & Chronic DIAIH with serum autoantibodies (+ ANA, + SMA, etc.)
  • e.g. nitrofurantoin, minocycline, methyldopa, hydralazine

• Cytokine agonists / inhibitors
  • e.g. infliximab, β-interferon

• Checkpoint inhibitors
  • e.g. Ipilimumab, nivolumab, pembrolizumab, atezolizumab

• Anti-T cell therapies
  • e.g. Daclizumab HYP
Inducing Autoimmunity – Challenge

Use of checkpoint inhibitors for oncotherapy

- Monoclonal inhibitors of CTLA-4, PD-1 or PD-1 receptors: Currently approved products include ipilimumab, nivolumab, pembrolizumab & atezolizumab
- Linked to high risk for autoimmune organ injuries mediated by ‘souped-up’ auto-reactive T & NK cells
- Characteristic auto-Abs not typically detected
- Autoimmune injuries: colitis > SCAR, hepatitis/ALF, endocrine organs, nephritis & other organs with comparatively short latencies after treatment initiation
- Risk levels for life-threatening AEs including severe immune-mediated hepatitis (IMH) is sufficiently high for valuable assessment in clinical efficacy trials
Immune-mediated Hepatitis (IMH)  
Checkpoint inhibitor-associated DILI

- IMH identified in clinical trials as serious complication
- Can progress to acute liver failure and death
- Clinical onset after initiation of treatment often within a few cycles (1-3 months) but ranges widely; Can recur with renewed treatment
- Liver Bx shows panlobular lymphocytic infiltrates & necrosis
- Product labels of checkpoint inhibitors contain warnings of IMH with liver monitoring instructions & risk management actions, including immediate treatment discontinuation procedures & treatment with corticosteroids or other immunosuppressive agents
- IMH susceptibility factors remain undefined
  - Pro-inflammatory localized interactions between metastatic tumor cell antigens & activated T-cells?
  - Unmasking of subclinical idiopathic autoimmune diathesis?
Checkpoint Inhibitors

Post-market: Life-threatening autoimmune AEs

• In first 3 yrs of ipilimumab marketing – Serious AE reports submitted to FAERS (crude nos):
  • Colitis ~ 380 reports
    • Some reports of intestinal perforation
  • Autoimmune hepatitis &/or Hepatic Failure ~ 50 reports
    • Liver metastases (melanoma) often present
    • Onset after a small no of q3wk infusions
    • Some reports of fatal outcomes with rapidly deteriorating liver function
60 yr old Male

- Melanoma metastases, brain & liver (2 lesions < 3cm, abd CT scan)
- Given 2 doses of ipilimumab (3mg/kg), 3 wks apart
- 3 wks after 2nd dose: Pt admitted with new onset weakness, diarrhea, tea colored urine & hepatic encephalopathy
- Began po 80 mg Prednisone & Lactulose
- 2 d later: IV methylprednisolone 100 mg bid, N-AC & Rifaxamin; Serum liver tests worsened
- Pt died in liver failure 5 days after admission
Personalizing Use of Checkpoint Inhibitors

Aiming for an Autoimmune ‘Goldilocks Zone’
Daclizumab HYP (DAC HYP)

MS Clinical Trial AIH Cases

• IgG1 monoclonal Il-2 receptor inhibitor of CD-25+ effector T-cells including those targeting the myelin sheath

• Also inhibitor of Fox-3+ CD-25+ regulatory T-cells (T regs) with unintended paradoxical auto-immune side-effects
  • After cessation of DAC HYP, the recovery of T-regs is gradual (5-6 mo) & can extend beyond the recovery time of autoreactive T-cells. This may explain the long time to onset of certain autoimmune AEs

• FDA Approved for Relapsing MS in pts with inadequate responses to 2 other agents

• Label contains boxed warning for liver failure, AIH & other autoimmune disorders

Drugs@FDA: Zinbryta; Other Reviews p. 164-186
Autoimmune Clinical Signature

**DAC HYP-associated DILI**

- Among 2,003 DAC-treated study subjects in safety population
  - one case of FHF (causally-related*)
  - 11 cases of liver injury causally-related* to DAC HYP marked by peak ALT increases ≥ 10X ULN and/or > 3X ULN with T Bili ≥ 2X ULN
- Median time to onset after start of DAC HYP – **13 mo**
- 6/11 cases identified as DAC HYP-related AIH
  - Long time to onset of AIH ~ **15 mo** (range 4 – 49 mo)
  - Negative ANA in 5/7 AIH cases)
  - Gradual recovery times, steroid responsive
- In SELECT, a randomized phase IIB study, 4% Daclizumab HYP randomized subjects had peak ALT elevations > 5X ULN, compared with < 1% in the placebo arm

*Causality with DAC-HYP assessed by FDA review as ‘probable’*
Assessment of DILI Risk

**RUCAM: Key Algorithmic Components**

- **Risk Components**
  - DILI association previously identified
  - Drug-associated causality (differential dx)
  - Clinical severity
  - Temporal features

- **Risk factors**
  - Only a few (e.g. age, alcohol, pregnancy)
# CIOMS Diagnostic Scale *(RUCAM)*

<table>
<thead>
<tr>
<th>Individual Criteria</th>
<th>Range of Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time from start of Rx until event</td>
<td>+1 to +2</td>
</tr>
<tr>
<td>Time from stop of Rx until event</td>
<td>0 to +1</td>
</tr>
<tr>
<td>Course after stop of Rx</td>
<td>-2 to +3</td>
</tr>
<tr>
<td>Age</td>
<td>0 to +1</td>
</tr>
<tr>
<td>Alcohol/Pregnancy</td>
<td>0 to +1</td>
</tr>
<tr>
<td>Concomitant Rx</td>
<td>-3 to 0</td>
</tr>
<tr>
<td>Non drug-related causes</td>
<td>-3 to +2</td>
</tr>
<tr>
<td>Previous drug information</td>
<td>0 to +2</td>
</tr>
<tr>
<td>Dechallenge/Rechallenge</td>
<td>-2 to +3</td>
</tr>
</tbody>
</table>

## Causality Assessment: Total Scores

Highly Probable: 8-10; Probable: 6-8; Possible: 3-5; Unlikely: 1-2

*Danan & Benichou, J. Clin. Epidemiol.; 1993*
## CIOMS Diagnostic Scale (RUCAM)

### Time Course Elements

<table>
<thead>
<tr>
<th>Type of Liver Injury</th>
<th>Hepatocellular</th>
<th>Cholestatic/Mixed</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Time of Onset of the Event</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Exposure</td>
<td>Second Exposure</td>
<td>First Exposure</td>
<td>Second Exposure</td>
</tr>
<tr>
<td>5 to 90 Days</td>
<td>1 to 15 Days</td>
<td>5 to 90 Days</td>
<td>1 to 90 Days</td>
</tr>
<tr>
<td>&lt;5 or &gt;90 Days</td>
<td>&gt;15 Days</td>
<td>&lt;5 or &gt;90 Days</td>
<td>&gt;90 Days</td>
</tr>
<tr>
<td><strong>Time from Drug Intake Until Reaction Onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 to 90 Days</td>
<td>1 to 15 Days</td>
<td>5 to 90 Days</td>
<td>1 to 90 Days</td>
</tr>
<tr>
<td>&lt;5 or &gt;90 Days</td>
<td>&gt;15 Days</td>
<td>&lt;5 or &gt;90 Days</td>
<td>&gt;90 Days</td>
</tr>
<tr>
<td><strong>Time from Drug Withdrawal Until Reaction Onset</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤15 Days</td>
<td>≤15 Days</td>
<td>≤30 Days</td>
<td>≤30 Days</td>
</tr>
<tr>
<td>≥30 Days</td>
<td>≥30 Days</td>
<td>&gt;30 Days</td>
<td>&gt;30 Days</td>
</tr>
<tr>
<td><strong>Risk Factors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Alcohol or Pregnancy</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>Age ≥ 55 Years</td>
<td>Age ≥ 55 Years</td>
<td>+1</td>
<td></td>
</tr>
<tr>
<td>&gt;50% Improvement 8 Days</td>
<td>—</td>
<td>+3</td>
<td></td>
</tr>
<tr>
<td>&gt;50% Improvement 30 Days</td>
<td>&gt;50% Improvement 180 Days</td>
<td>+2</td>
<td></td>
</tr>
<tr>
<td><strong>Course of the Reaction</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lack of Information or No Improvement</td>
<td>Lack of Information or No Improvement</td>
<td>+0</td>
<td></td>
</tr>
<tr>
<td>Worsening or &lt;50% Improvement 30 Days</td>
<td>—</td>
<td>-1</td>
<td></td>
</tr>
</tbody>
</table>
Drug X: Benefits vs DILI Risk

*RUCAM vs time to DILI onset*

- **RUCAM:** +2 Points

*Scale is for hypothetical discussion & has no regulatory inference*
Drug Y: Benefits vs DILI Risk

*RUCAM vs time to DILI onset*

RUCAM: +2 Points

*Scale is for hypothetical discussion & has no regulatory inference*
Drug Z: Benefits vs DILI Risk

**RUCAM vs time to DILI onset**

RUCAM: +2 Points

*Scale is for hypothetical discussion & has no regulatory inference*
Summary

• Acute hepatocellular DILI is associated with different clinical signatures determined by distinct underlying mechanisms of toxicity.

• To assess benefits & risks, agent-related DILI risk profiles must include evaluation of incidence, range of clinical severity, causality & temporal characteristics of the liver injury. An assessment of benefits must also take into account basic temporal characteristics associated with a treatment agent.

• The current version of RUCAM is a ‘one-size shoe fits all’ which does not take into account important differences in mechanisms & clinical signatures of acute liver cell injury caused by different agents. An ongoing challenge is aligning algorithmic scoring rules with an appropriate set of agent-related DILI risk criteria.
FDA DILI website: www.fda.gov/Drugs/ScienceResearch/ResearchAreas