Assessing Hepatoxicity of Drugs & Biologicals

A Challenge for Regulatory Science

November 15, 2018

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

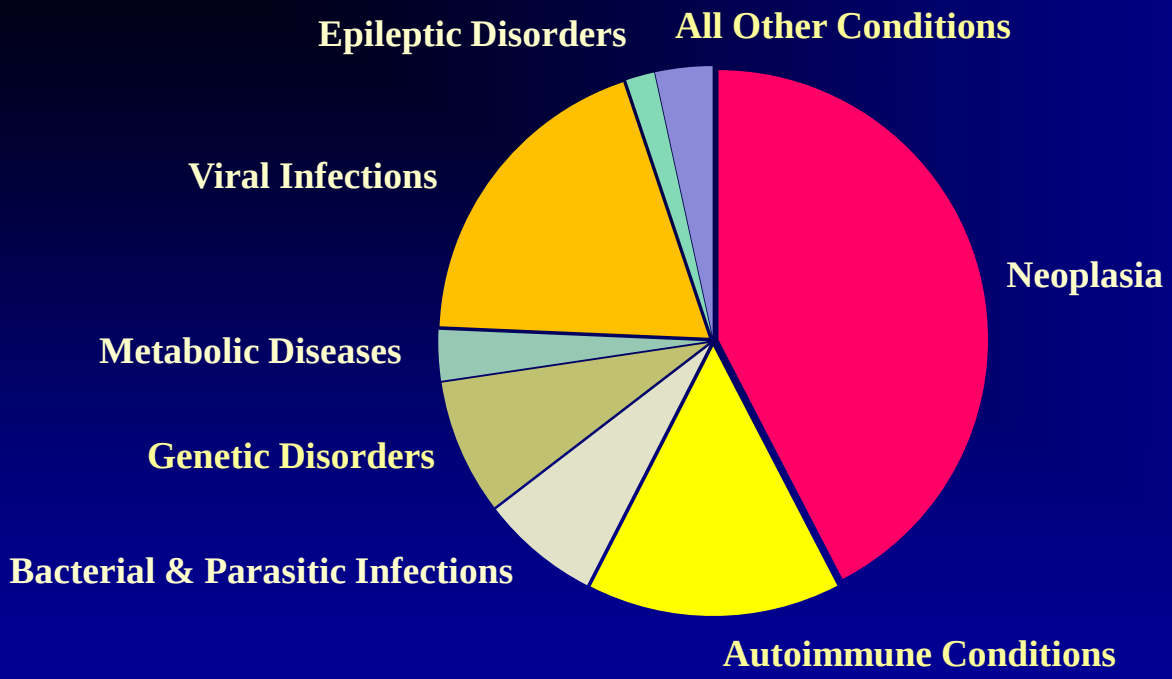
Hyman Zimmerman
1914-1999

NIH Liver Club; Bethesda, MD - 1985

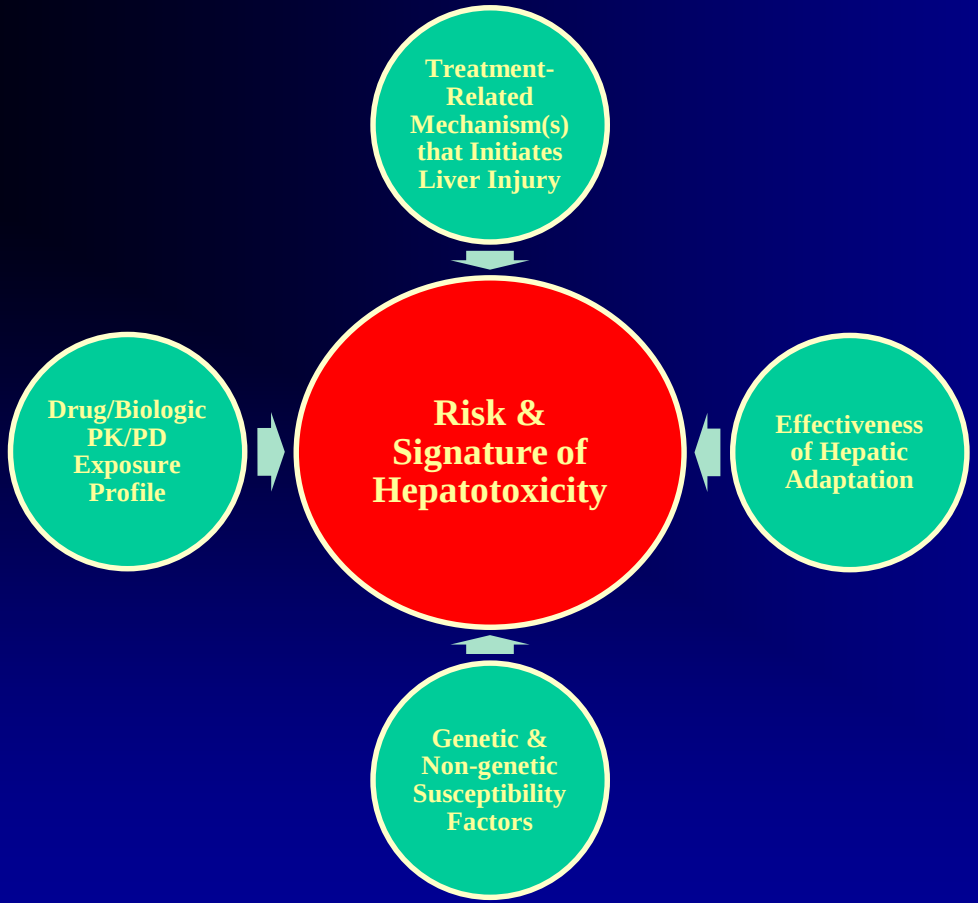
John Senior; FDA - 2017

Novel FDA - Approved Drugs & Biological Agents with Hepatotoxicity Warnings (N=59)*

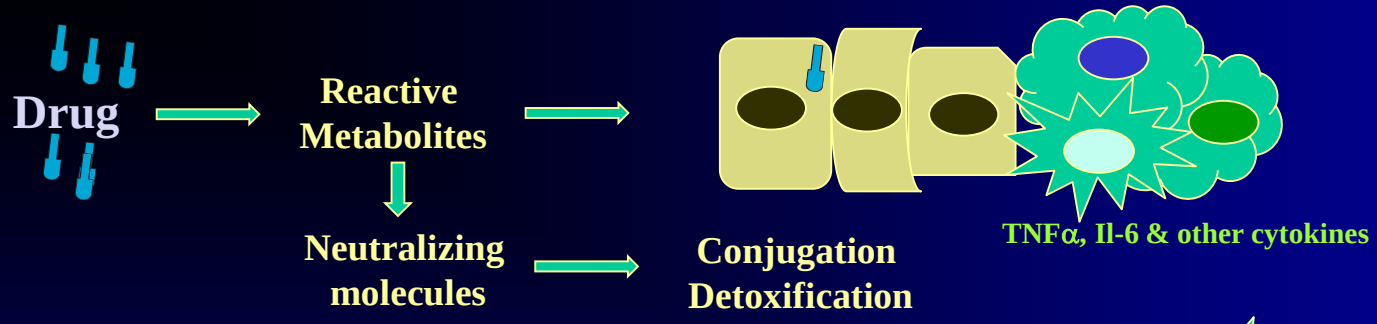
Distribution Among Disease Treatment Categories



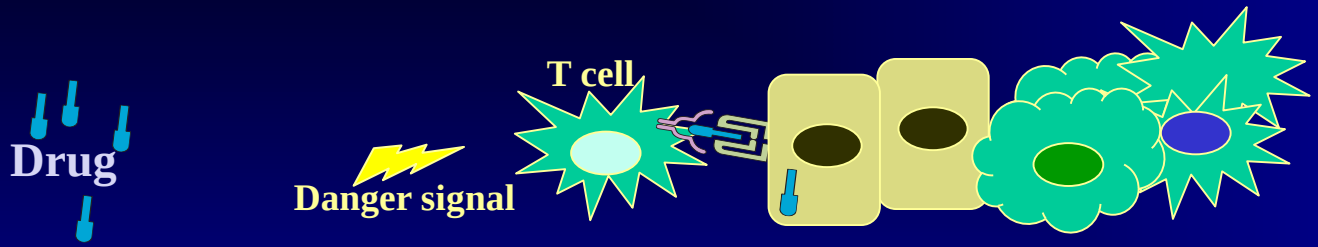
*Approved by FDA January 2012 – July 2017; 30% of all the novel agents (N=197) approved in that period.
https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/default.htm


Treatment-Related Mechanism(s) that Initiates Liver Injury
Drug/Biologic PK/PD Exposure Profile
Risk & Signature of Hepatotoxicity
Effectiveness of Hepatic Adaptation
Genetic & Non-genetic Susceptibility Factors

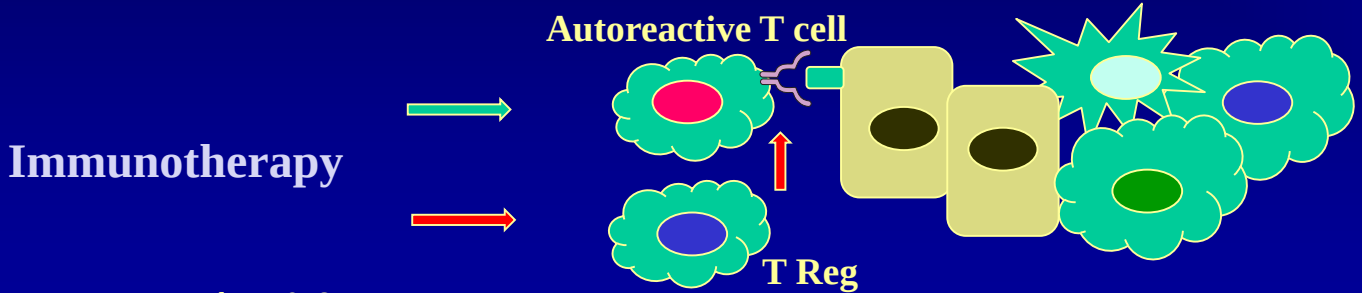
Mechanisms that may trigger DILI



Oxidative stress
Mitochondrial injury
BSEP inhibition



Adaptive immune response



Autoimmunity & AIH

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]**

Levels of DILI Severity

5	Death/Tx
4	Acute Liver Failure
3	Serious: Disabled, Hospitalized
2	Detectable Slight Functional Loss
1	Serum Enzyme Elevations Only; Many People Adapt
0	Most People Tolerate Exposure - No Adverse Effects Seen

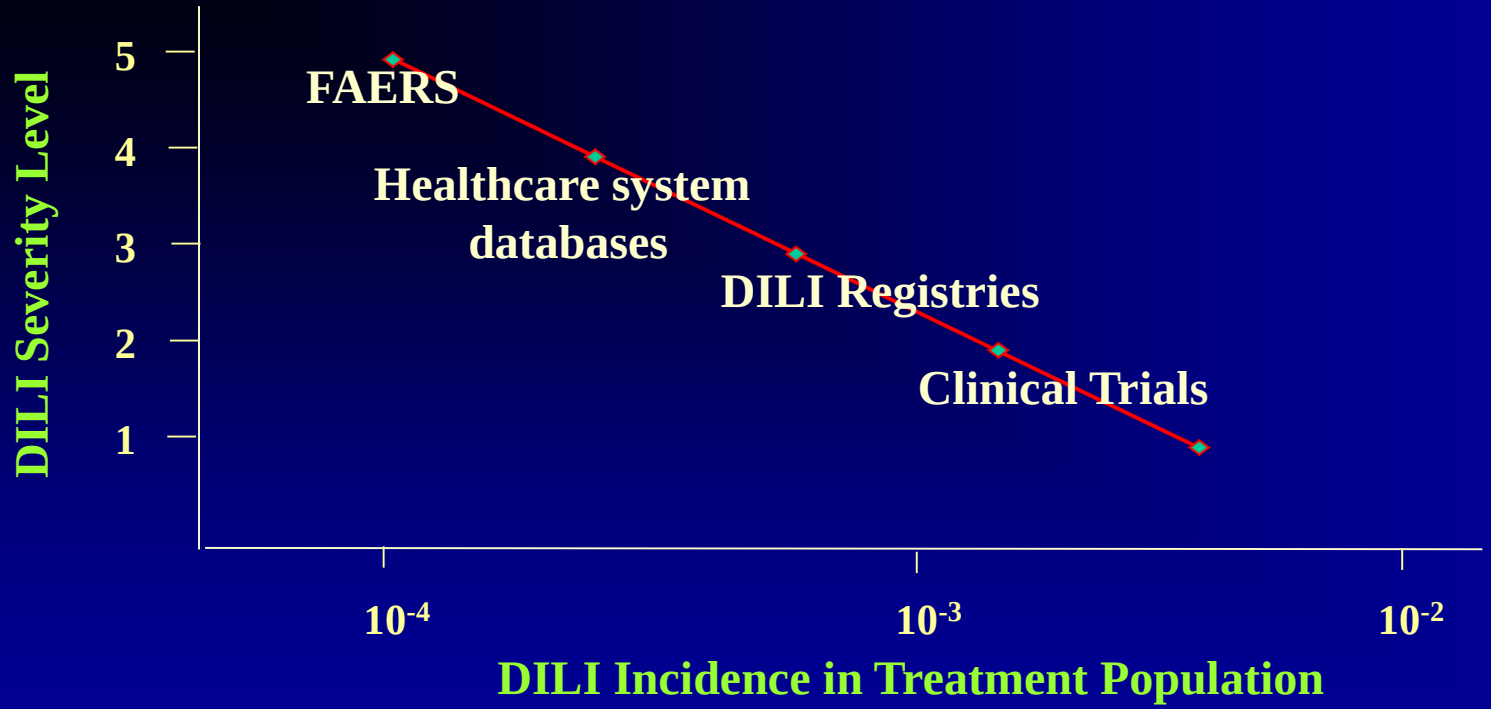
DILI Risk Profile in Exposure Population

Questions with regulatory impact

- Does the drug cause clinically significant DILI in the target treatment population?
- What is the clinical signature of injury associated with the drug?
- What ranges of dose & duration of exposure are associated with increased risk?
- What are the critical patient susceptibility factors?
- What incidences of mild & severe liver injury can be predicted in a large treatment population?

Detection of Idiosyncratic DILI

Utility of Clinical Data Sources



Identifying a DILI Signal
Clinical Trials

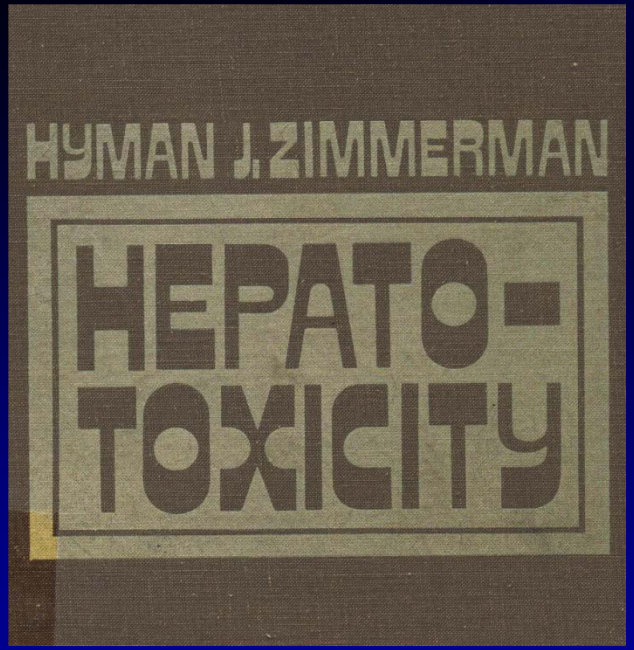
Finding of liver injury associated with exposure to a drug which may indicate an increased risk for life-threatening injury in others exposed to the same drug

1 – Imbalance of liver injuries in randomized trials: active drug vs placebo; events may be mild and transient

- Often reflect adaptation after initiation of injury
- Spectrum of clinical severity in larger exposure population may be difficult to predict

2 - Clinically significant DILI cases

- Marked by symptoms, jaundice, &/or coagulopathy
- Causality analysis is critical in characterization of signal



1st Edition, Appleton-Century Crofts, 1978

Chapter 16

DRUG-INDUCED LIVER DISEASE

IMPORTANCE OF DRUG-INDUCED INJURY

Adverse reactions to drugs account for only a small fraction of cases of overt liver disease. Only 2 percent of patients with jaundice admitted to general hospitals in Boston[8] and in Copenhagen[9] were considered to have drug-induced liver disease (Fig. 16.2). Among special populations, however, the relative importance of drug-induced hepatic injury is greater. In one geriatric hospital, reactions to drugs appeared to be responsible for 20 percent of instances of jaundice,[10] and in hospitals with a high proportion of patients receiving psychoactive[11] or antituberculosis[12] drugs, the relative incidence might also be higher.

As a cause of massive hepatic necrosis, drug-induced hepatic injury plays an important role (Fig. 16.3). Among the causes of fulminant hepatic failure recorded by Trey and Davidson,[13] Caravetti and his associates,[14] and Ritt et al,[15] reactions to medicinal agents accounted for 20 to 30 percent of cases. The seemingly paradoxical disparity between the relatively small proportion of all cases of jaundice attributable to drugs and the major importance of drug-induced injury as a cause of acute hepatic failure finds ready explanation in the gravity of drug-induced injury of the hepatocellular type.[2] The case fatality rate ranges from 10 to 50 percent (Table 16.1).[2] Thus, the severity of drug-induced hepatocellular injury

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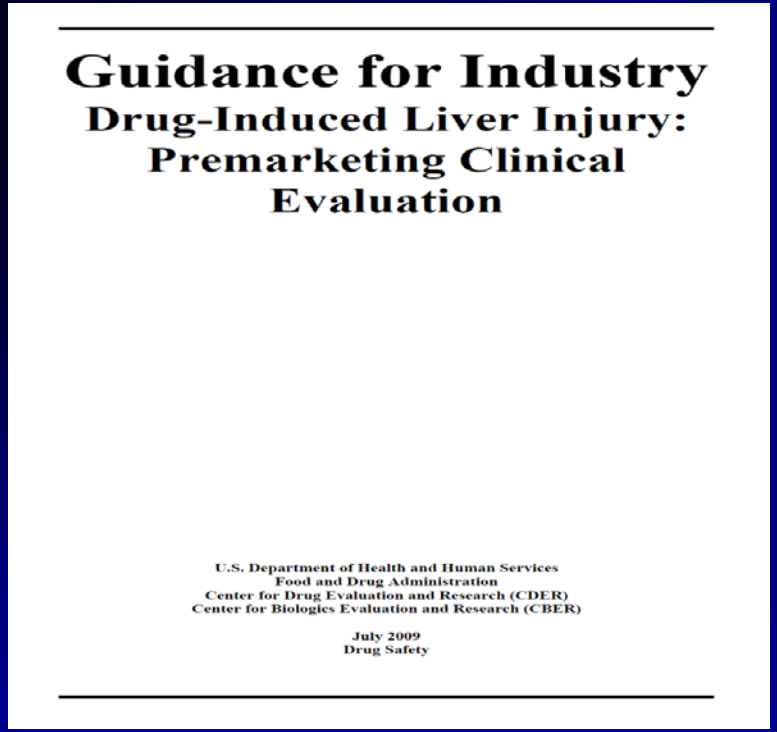


Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety

www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf

DILI Guidance: Premarketing Clinical Evaluation

Assertions

- Withdrawn hepatotoxic drugs: DILI-related death or liver transplant may be ≤ 1,5000-1/10,000; May not occur in clinical trials

- Isolated imbalance of serum ALT/AST elevations (drug vs placebo): Low specificity to predict serious DILI

- Hy's Law Cases: Strong Positive Predictive Value for ↑Risk of ALF
  - Total Bili > 2X ULN
  - ALT/AST > 3X ULN
  - Alk Phos < 2X ULN, R [ALT/Alk Phos (Fold ULN)] > 5
  - Other etiologies of acute liver injury excluded!

    (e.g. *Acute viral hepatitis, Autoimmune hepatitis, Alcoholic hepatitis, Biliary disorder, cardiovascular hepatopathy, alpha-1-antitrypsin deficiency, Wilson's disease, Another hepatotoxic drug or dietary supplement)*

DILI Guidance: Premarketing Clinical Evaluation

Hy's Law & Clinical Correlates

- Hepatotoxic drugs & Hy's law
  - 10-50% case mortality with hepatocellular form of DILI injury associated with jaundice; confirmed by recent large studies*
  - 'Rule of 3': Absence of Hy's law cases in n study subjects excludes risk above n/3
  - drug development program examples: dilevalol, 2/1,000; troglitazone, 2/2,500
- Hepatotoxic drug without Hy's law signatures (examples)
  - perhexilene: EtOH-like injury
  - fialuridine: metabolic acidosis;
  - valproic acid: microvescicular steatosis;
  - benoxaprofen: intrahepatic cholestasis;
  - minocycline: autoimmune hepatitis, immunoallergic injury or steatosis

* Andrade et al., Gastro. 2005; Bjornsson & Olsson, Hepatology, 2005

DILI Guidance

Evaluation & Management Steps in Clinical Trials

- characterization of baseline liver conditions/diseases
- efficient detection of acute liver injury (early symptoms, systematic serum lab tests)
- confirmation with repeat testing
- observation & workup of patients with liver injury
- consensus study *stop rules*
  - ALT/AST > 8X ULN
  - ALT/AST remains > 5X ULN over 2 wks
  - ALT/AST > 3X ULN & T Bili > 2X ULN or INR > 1.5
  - ALT/AST > 3X ULN with symptoms (e.g. fatigue, N&V, RUQ pain, fever, rash) or eosinophilia
  - *rechallenge* generally should be avoided with ALT/AST > 5X ULN unless no other good therapeutic options, informed consent encouraged

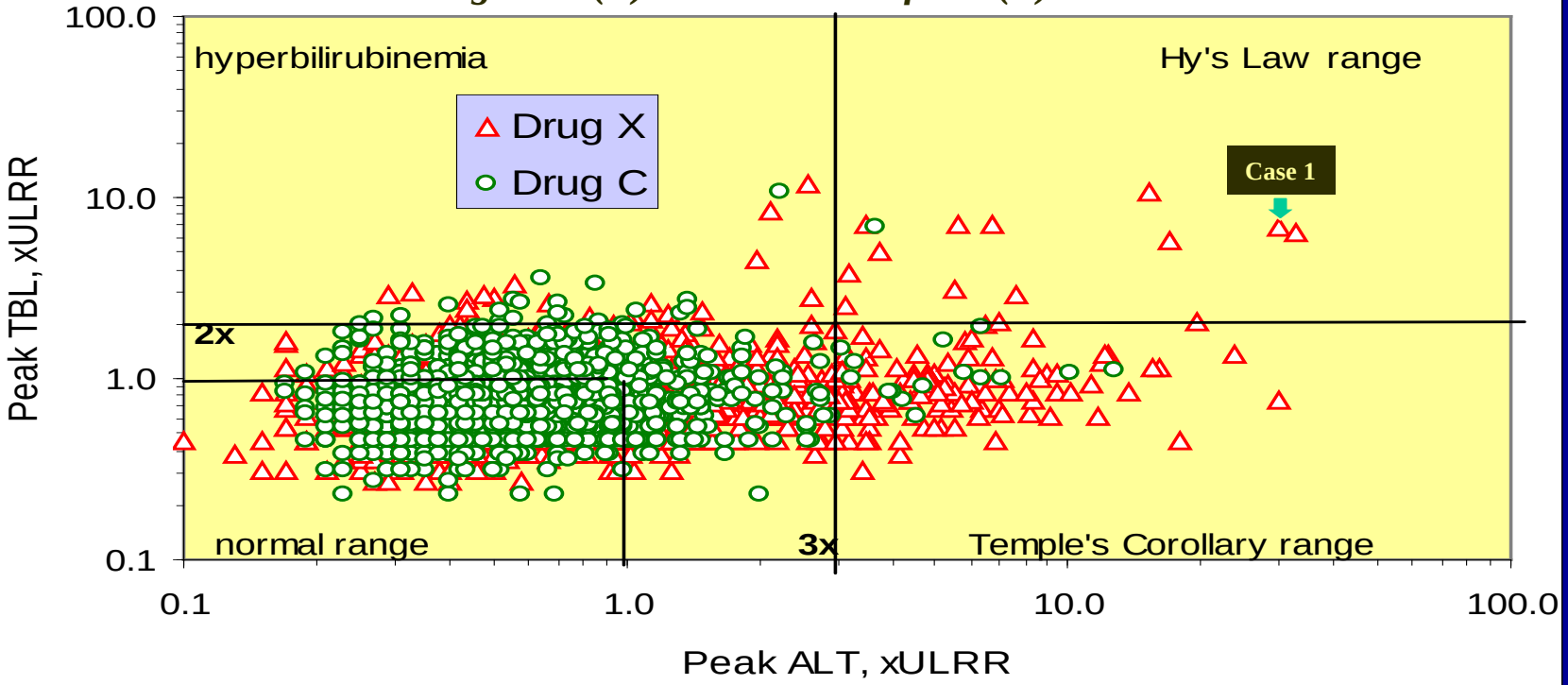
‘Classic’ Signature of Idiosyncratic DILI

DILI in Clinical Trials

- Ximelagatran is prodrug of melagatran – induces acute hepatocellular necrosis
- Not approved in US & withdrawn elsewhere
- 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

“eDISH” Peak Liver Tests: SPORTIF V

Ximelagatran (X) n=1821 vs Warfarin (C) n = 1927



http://www.FDA.gov/CDER/LiverTox

Case 1: 80 yr old male*

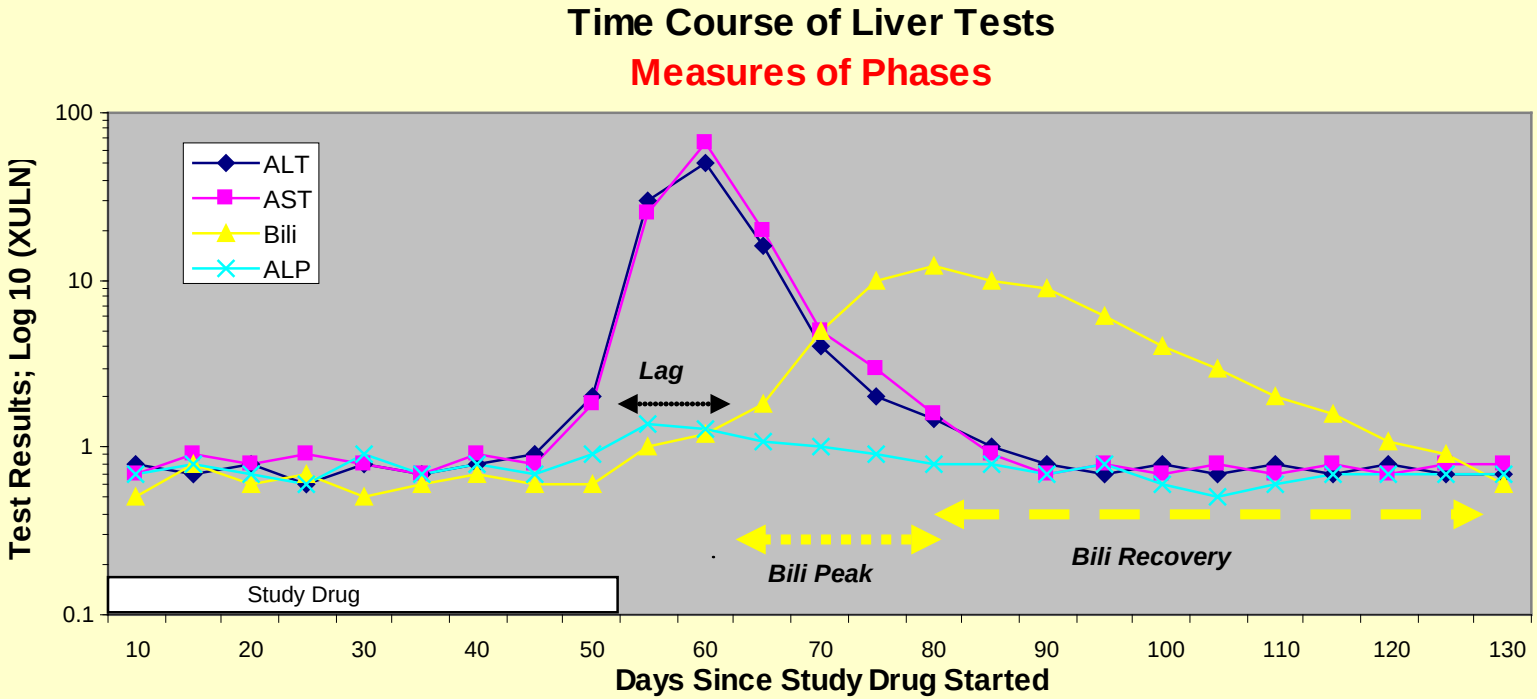
Day	Event
1	ALT: 16 U/L, *Start ximelagatran 36 mg bid for AFib*
30	ALT: Normal
56	ALT: 2X ULN
85	ALT: 20X ULN; T. Bilirubin 1.1 mg/dL; *Stop ximelagatran*
100	ALT: 30X ULN; T. Bili 2.4 mg/dL; AP 154 U/L; Serologic testing for Hepatitis A, B, C, CMV, EBV, HSV, CEA, ANA, liver imaging all unremarkable
108	Liver Bx: Acute submassive necrosis
114	INR: 1.7, Alb 2.9 g/dL, T. Bili 10.7 mg/dL, PT 16.3 seconds
119	INR: 1.8, Alb 2.5 g/dL, T. Bili 17.1 mg/dL
145	Died: duodenal ulcer bleed with coagulopathy

Autopsy: small, friable and diffusely mottled liver with extensive liver necrosis, hepatocyte dropout and bile duct proliferation

*Adapted from M Desai (2004) Review: *https://www.fda.gov/ohrms/.../2004-4069B1_06_FDA-Backgrounder-C-R-MOR.pdf*

Biochemical Patterns of Recovery / Progression

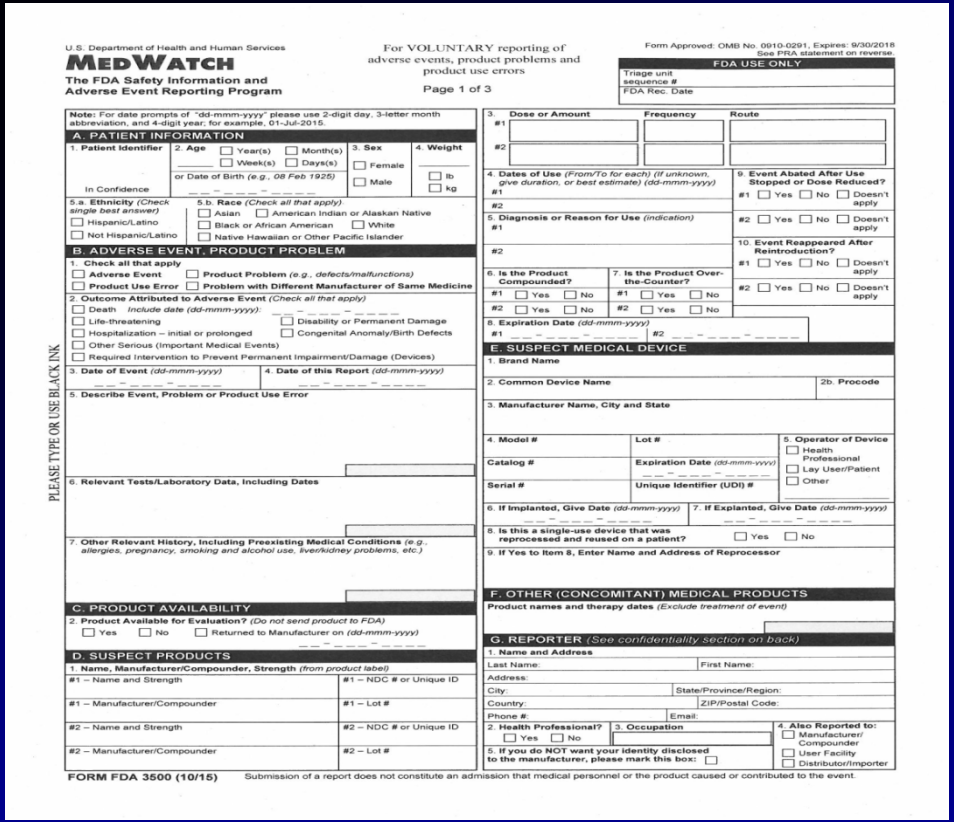
DILI profile with prolonged cellular recovery



Drug Life-Cycle Data Streams

Post-market DILI Risk Assessment

- MedWatch/FAERS reports
- Published case reports
- DILI registries
- Sentinel System
- Epidemiological databases
  - Observational cohort studies
  - Case-control studies



U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

For VOLUNTARY reporting of adverse events, product problems and product use errors

Page 1 of 3

Form Approved: OMB No. 0910-0291, Expires: 9/30/2018
See PRA statement on reverse.

FDA USE ONLY
Triage unit
sequence #
FDA Rec. Date

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2015.

A. PATIENT INFORMATION

1. Patient Identifier — In Confidence
2. Age — Year(s) Month(s) Week(s) Day(s) or Date of Birth (e.g., 08 Feb 1925)
3. Sex — Female Male
4. Weight — lb kg

5.a. Ethnicity (Check single best answer) — Hispanic/Latino; Not Hispanic/Latino

5.b. Race (Check all that apply) — Asian; American Indian or Alaskan Native; Black or African American; White; Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM

1. Check all that apply — Adverse Event; Product Problem (e.g., defects/malfunctions); Product Use Error; Problem with Different Manufacturer of Same Medicine

2. Outcome Attributed to Adverse Event (Check all that apply) — Death Include date (dd-mmm-yyyy); Life-threatening; Hospitalization – initial or prolonged; Other Serious (Important Medical Events); Required Intervention to Prevent Permanent Impairment/Damage (Devices); Disability or Permanent Damage; Congenital Anomaly/Birth Defects

3. Date of Event (dd-mmm-yyyy)

4. Date of this Report (dd-mmm-yyyy)

5. Describe Event, Problem or Product Use Error

6. Relevant Tests/Laboratory Data, Including Dates

7. Other Relevant History, Including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)

C. PRODUCT AVAILABILITY

2. Product Available for Evaluation? (Do not send product to FDA) — Yes No Returned to Manufacturer on (dd-mmm-yyyy)

D. SUSPECT PRODUCTS

1. Name, Manufacturer/Compounder, Strength (from product label)

#1 – Name and Strength	#1 – NDC # or Unique ID
#1 – Manufacturer/Compounder	#1 – Lot #
#2 – Name and Strength	#2 – NDC # or Unique ID
#2 – Manufacturer/Compounder	#2 – Lot #

3. Dose or Amount / Frequency / Route — #1, #2

4. Dates of Use (From/To for each) (If unknown, give duration, or best estimate) (dd-mmm-yyyy) — #1, #2

5. Diagnosis or Reason for Use (indication) — #1, #2

6. Is the Product Compounded? — #1 Yes No; #2 Yes No

7. Is the Product Over-the-Counter? — #1 Yes No; #2 Yes No

8. Expiration Date (dd-mmm-yyyy) — #1, #2

9. Event Abated After Use Stopped or Dose Reduced? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

10. Event Reappeared After Reintroduction? — #1 Yes No Doesn't apply; #2 Yes No Doesn't apply

E. SUSPECT MEDICAL DEVICE

1. Brand Name
2. Common Device Name — 2b. Procode
3. Manufacturer Name, City and State
4. Model # / Lot # / Catalog # / Expiration Date (dd-mmm-yyyy) / Serial # / Unique Identifier (UDI) #
5. Operator of Device — Health Professional; Lay User/Patient; Other
6. If Implanted, Give Date (dd-mmm-yyyy)
7. If Explanted, Give Date (dd-mmm-yyyy)
8. Is this a single-use device that was reprocessed and reused on a patient? Yes No
9. If Yes to Item 8, Enter Name and Address of Reprocessor

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

Product names and therapy dates (Exclude treatment of event)

G. REPORTER (See confidentiality section on back)

1. Name and Address — Last Name: First Name: Address: City: State/Province/Region: Country: ZIP/Postal Code: Phone #: Email:
2. Health Professional? Yes No
3. Occupation
4. Also Reported to: Manufacturer/Compounder; User Facility; Distributor/Importer
5. If you do NOT want your identity disclosed to the manufacturer, please mark this box:

PLEASE TYPE OR USE BLACK INK

FORM FDA 3500 (10/15) Submission of a report does not constitute an admission that medical personnel or the product caused or contributed to the event.

MedWatch Reports

Reports of suspected DILI that provide clinically informative narratives & adequate diagnostic information to exclude potential causes other than the suspect drug are critically important tools in the public health domain.

Reporter's confidentiality & Patient's privacy are both protected by FDA rules. HIPAA rules recognize the need for public health authorities to have access to information regards patient safety.

https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home

Case Causality Analysis of Liver Injury

Important Information Components

- Time to onset after starting the drug
- Time to recovery after stopping the drug
- Clinical pattern including injury phenotype & severity
- Exclusion of alternative causes of liver injury
- Recognition whether drug is associated with liver injury
- Identified DILI susceptibility factors
- Determination of response to re-exposure, if performed

Methods to Determine Causality

- RUCAM & Other Algorithmic Approaches
- Expert Opinion
- Probabilistic/Bayesian Techniques

CIOMS Diagnostic Scale *(RUCAM)**

Hepatocellular Injury

Individual Criteria	*Maximum Score*
• Time from start of suspect drug until event (1st exposure)	5-90 days
• Time from stop of suspect drug until event	≤ 15 days
• ALT: > 50% improvement after stop suspect drug	< 8 days (from peak value)
• Age	> 55 years old
• Risk Factors	EtOH or pregnancy only
• Concomitant drug(s)	None known to cause DILI
• Non drug-related causes (sliding scale)	R/O all diagnoses in 2 groupings
• Previous drug information	++ DILI in product label / literature
• Rechallenge (despite potential DILI risk)	ALT : ≥ 2X

Causality Assessment: Total Scores (potential -5 to +14)

Highly Probable: > 8; Probable: 6-8; Possible: 3-5; Unlikely: 1-2; Excluded: ≤ 0

*Danan & Benichou, J. Clin. Epidemiol.; 1993

RUCAM: Applications & Limitations

- **Highest utility**
  - Post-market case assessment by bed-side practitioners
  - Suspect drug with recognized DILI association & stereotypical signature
- **Poor utility in clinical trials & drug development**
  - Instrument validated in a small cohort of individuals with positive re-challenge (n=49 vs 28)*
  - Some DILI phenotypes do not align with temporal criteria of the algorithm
  - Clinical & diagnostic information to rule out ALL alternative causes often missing
  - Culprit drug may not be reliably identified in presence of concomitant agents with hepatotoxic profiles
  - Inconsistent interrater variability & test-retest reliability
  - No flexibility for raters to weigh information that informs causality
  - Many drug-specific risk elements are not included in the algorithm

*Benichou C., Danan, G., & Flahault, A., J. Clin. Epidemiol. 1993

Expert Opinion

Basic Features

- Independent assessments by individuals with subject-matter expertise
- Structured consensus building process among panel of experts
- Used by regulatory scientists to assess clinical trial liver injury cases
  - Goals: 1) integrate all pre-clinical and clinical data for risk assessment prior to consideration of drug approval; 2) enhance post-market risk evaluation, communication & management

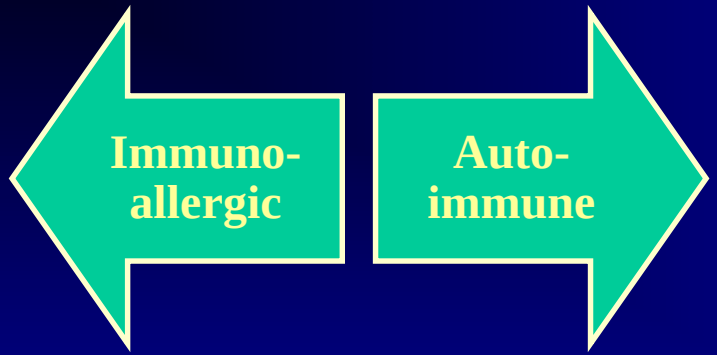
Advantages (despite absence of 'gold-standard' DILI biomarker)

- Permits recognition & assessment of wide range of hepatotoxic signatures (e.g. toxic injuries with short & long latencies to onset, hyper-acute & chronic patterns)
- Enables integration of new scientific information & assessment of mechanistic plausibility informed by different scientific disciplines
- Inter-rater variability mitigated by procedures to establish consensus
- Can promote structured data collection, & clinical trial protocol improvements

Liver Injury Caused by Therapeutic Drugs

Targets: drug-associated antigens or self

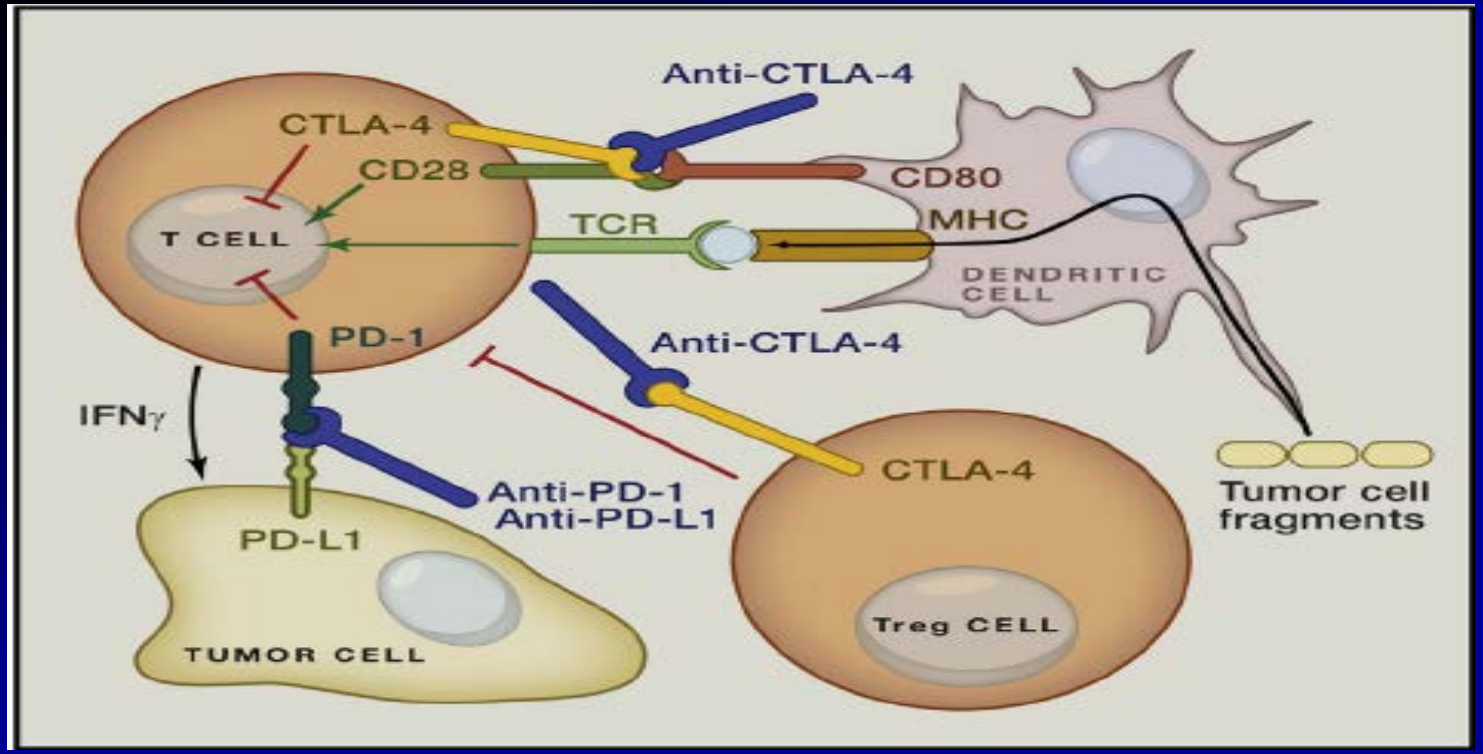
- Onset within 1-8 wks of treatment; can be as short as 1-2 days
- Other organs can be simultaneously affected
- Multiple types of hypersensitivity
- Fever, rash, eosinophilia common in some forms
- Re-challenge has significant risk



Reaction Pathways

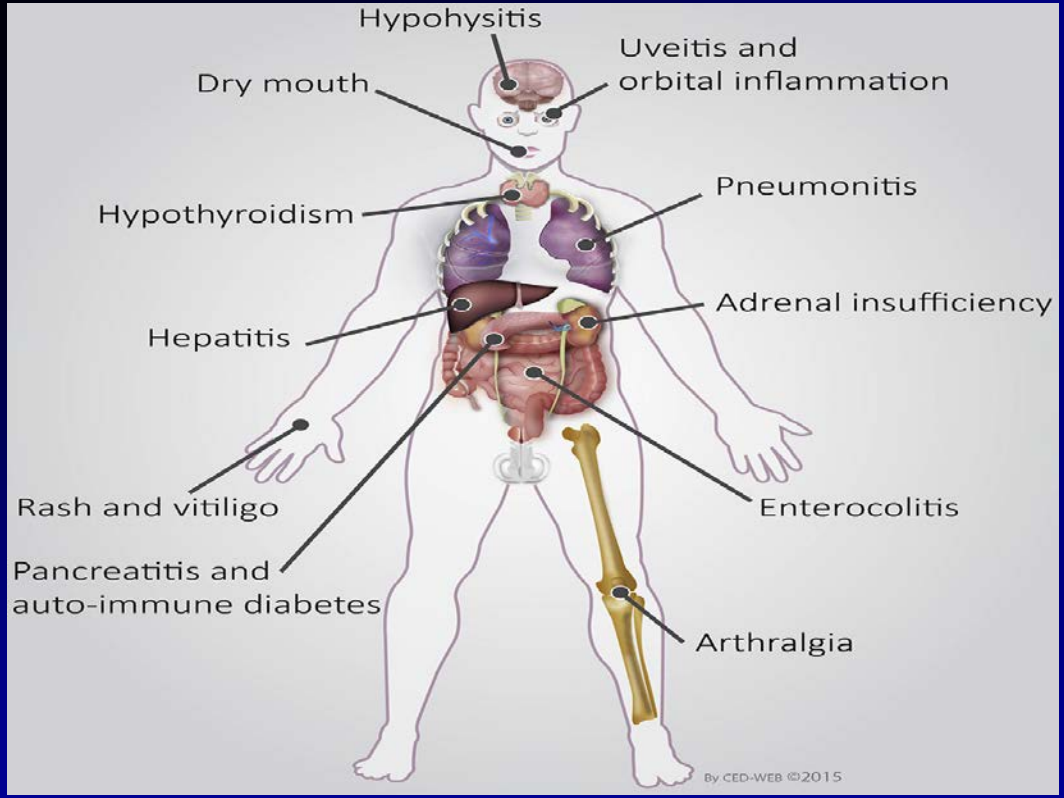
- Different latencies to onset after treatment initiation
- Acute, sub-acute or chronic liver injury phenotypes
- Sites of autoimmune injury related to the specific drug & individual susceptibility
- Not all drugs have characteristic autoantibody profiles

Antibody-Mediated Targeting of Negative Regulators of T Cell Responses



Miller and Sadelain, Cancer Cell, 27, 439-49, 2015

The Clinical Spectrum of Immune-Related Adverse Events Pertaining to Checkpoint Inhibition



Michot JM et al 2016

Immune-mediated Hepatitis (IMH)

Checkpoint inhibitor-associated DILI

- Currently FDA-approved: *Ipilimumab*, *nivolumab*, *pembrolizumab*, *atezolizumab*, *avelumab*, *durvalumab & cemiplimab*
- IMH identified in clinical trials
  - Severe IMH can progress to ALF
  - Clinical onset after initiation of treatment often within **1-3 months -** but ranges widely
  - Can recur with renewed treatment
- Product labels: Warnings of IMH include instructions for liver monitoring & risk management actions (e.g. discontinuation & treatment with corticosteroids or other agents)
- Susceptibility factors of concern
  - Combination therapies
  - Underlying auto-immune diathesis
  - Chronic infection
  - Pro-inflammatory interactions between infiltrating tumor cells & activated T-cells?

Post-market Case of Interest: 60 yr old male

- Melanoma metastases, brain & liver (abdominal CT scan: 2 lesions < 3cm)
- Administered 2 doses of *ipilimumab* (3mg/kg), 3 wks apart
- 3 wks after 2nd dose: Hospitalized with new onset weakness, diarrhea, tea colored urine & hepatic encephalopathy
  - ALT: 1704 U/L, AST: 3371 U/L, ALP: 886 U/L(baseline: 84), T. Bili: 5.1 mg/dL, LDH, >2500 U/L, US: heterogeneous liver, IgG: 699 mg/dL, IgM: 72 mg/dL, ANA: 27 U (not elevated), Viral serology: unremarkable
- Started po 80 mg Prednisone & Lactulose
- 2 d later: IV methylprednisolone 100 mg bid, N-AC & Rifaxamin; Serum liver tests worsened
- Died in liver failure 5 days after admission

MS Clinical Trial AIH Cases

- Daclizumab (DAC HYP): FDA-approved 5/27/2016 for Relapsing MS after inadequate response to 2 other agents; global withdrawal 3/2/2018 after PM cases of encephalitis
- Boxed warning: Liver failure, AIH & other autoimmune disorders
- IgG1 monoclonal Il-2 receptor inhibitor of CD-25+ effector T-cells including those targeting the myelin sheath
- Fox-3+ CD-25+ regulatory T-cells (T regs) also inhibited with unintended auto-immune side-effects*
  - After administration of DAC HYP, the recovery of T-regs is gradual (5-6 mo) & can extend after the recovery of autoreactive T-cells; May explain long time to onset of some autoimmune AEs

*Drugs@FDA: Zinbryta; Other Reviews p. 164-186

Autoimmune Clinical Signature

- Among 2,003 DAC HYP-treated study subjects in safety population (reviewed in NDA)
  - One case of FHF*
  - 11 cases of liver injury causally-related to DAC HYP marked by peak ALT increases $\geq$ 10X ULN and/or > 3X ULN with T Bili $\geq$ 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

*Causality with DAC-HYP assessed by FDA review as 'probable'

Unresolved Issues

- **Current instruments & biomarkers**
  - Do not reliably predict DILI risk early in drug development, irrespective of the drug or biological agent
  - Do not model all plausible drug-related toxic pathways in liver cells
- **Gaps in causality assessment**
  - Wide range of DILI mechanisms & clinical signatures
  - Pre-existing liver diseases & cirrhosis
  - Combination cancer treatments with additive toxicity
  - Treatment with herbal products & dietary supplements
  - Treatment with more than one hepatotoxic agent
- **Do we need one improved or multiple causality algorithms?**

FDA DILI Conference websites

www.aasld.org/2016-drug-induced-liver-injury-annual-conference-proceedings

www.fda.gov/Drugs/ScienceResearch/ResearchAreas/ucm071471.htm *(Archived)*