Drug-Induced Liver Injury (DILI)

CLINICAL INVESTIGATOR TRAINING COURSE
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John Senior offers his apologies for being in California on the date of this presentation, in order for him to attend annual meetings of the American Association for the Study of Liver Diseases. I have agreed to speak in his stead, and will relay questions and comments to him for replies. John and I have worked together for 10 years, organizing and hosting annual meetings each year in March, devoted to the topic of DILI, as the field advances and more is learned.

Opinions expressed do not reflect official policies or positions of the FDA, but are the author's personal opinions based on these diverse experiences.

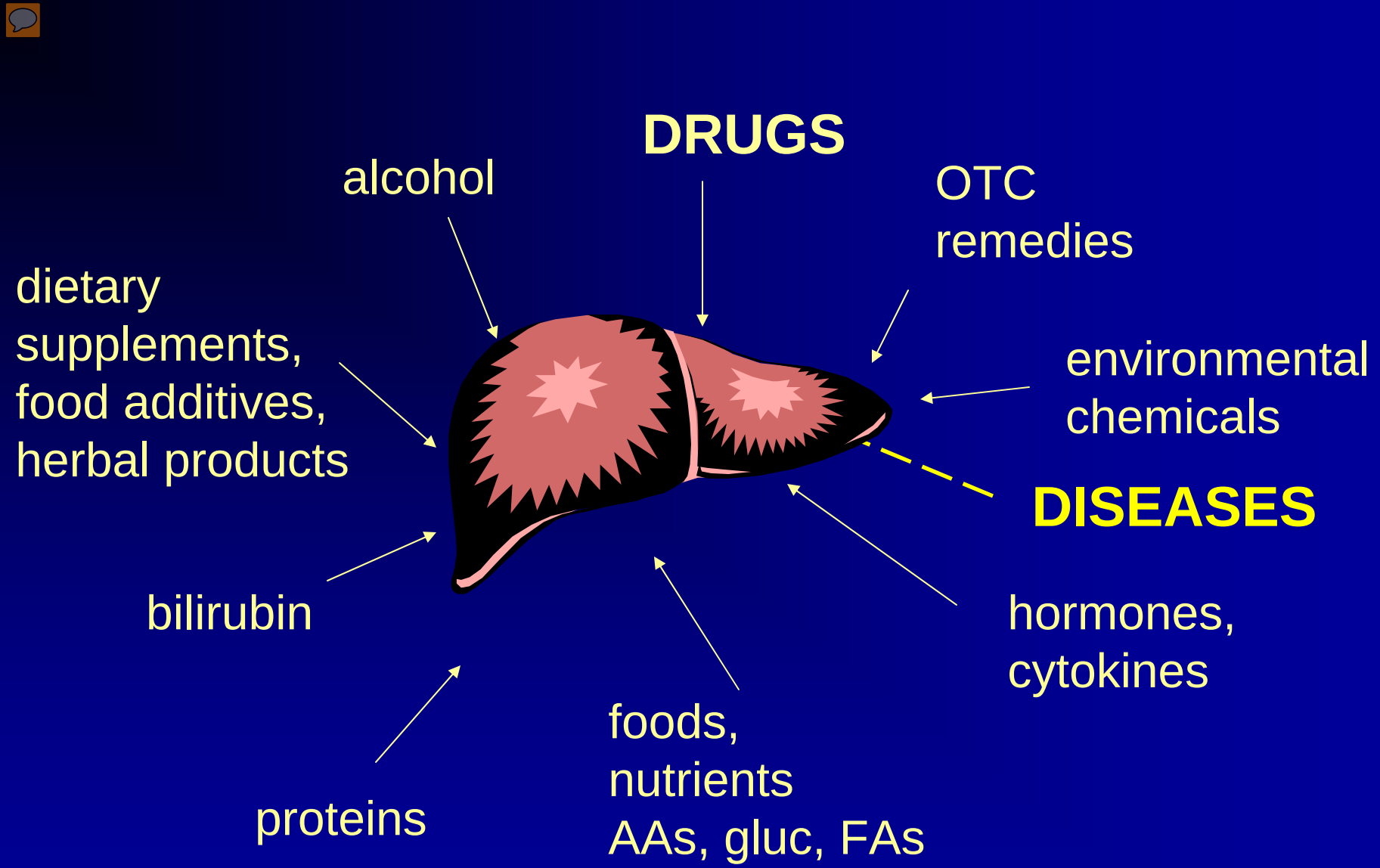
Why Should We Care about DILI?

1. Drugs used for therapeutic intent may cause serious or even fatal liver injury in some patients
2. Although usually rare, it may result in disapproval of a new drug or removal from the market
3. It's a troublesome problem for drug development, for regulatory agencies, and for patient care

What Does the Liver Do?

The liver is a remarkable organ that serves as the body's chemical engineering and control center, regulating the metabolism of internal compounds and coping with compounds coming in from the environment, such as DRUGS.

It has astounding ability to adapt, to change itself, to alter activities of its enzymes and transporters, and even to regenerate rapidly if cells are killed or removed.

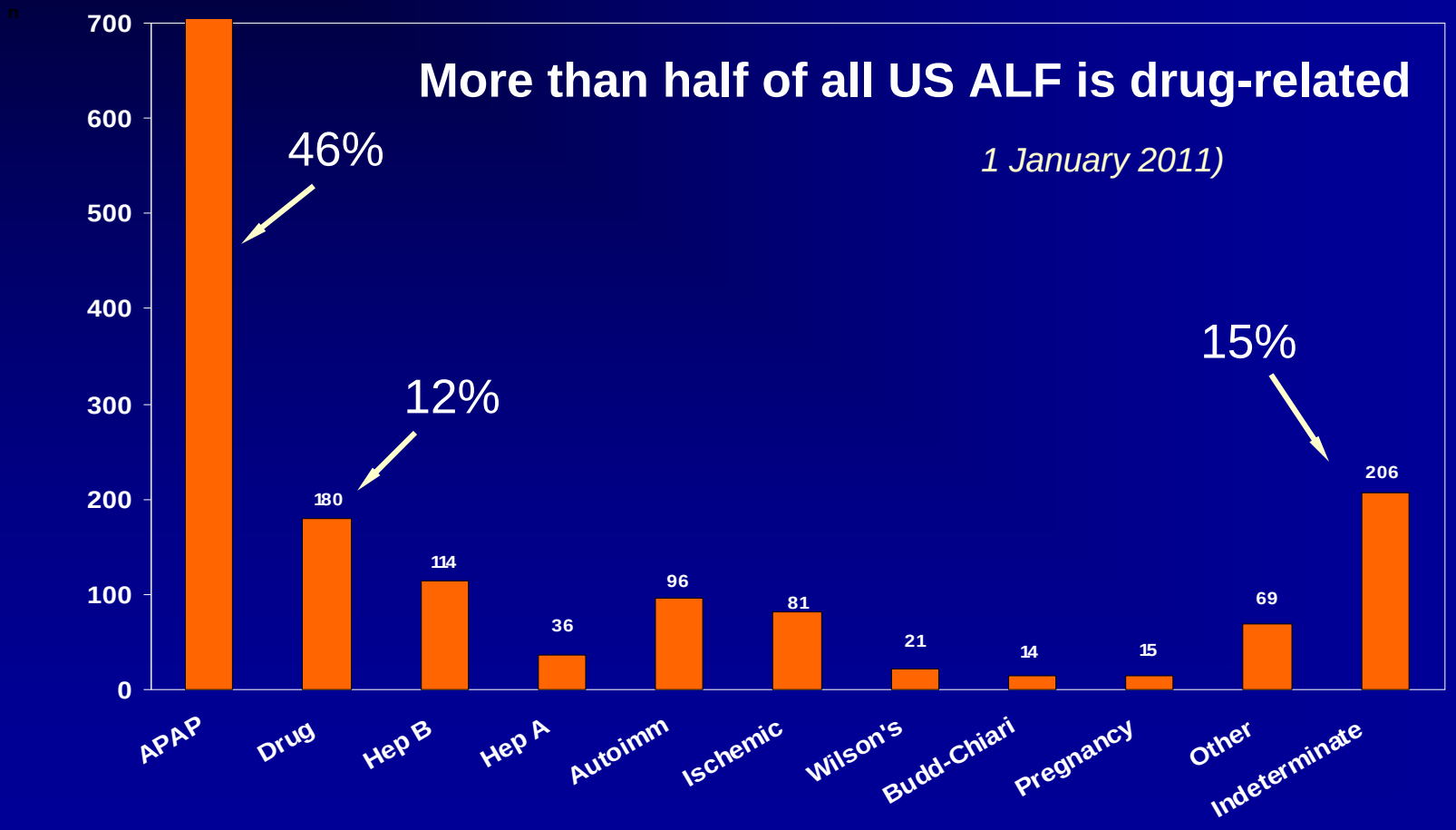

DRUGS
alcohol
OTC
remedies
dietary
supplements,
food additives,
herbal products
environmental
chemicals
DISEASES
bilirubin
hormones,
cytokines
foods,
nutrients
AAs, gluc, FAs
proteins

*Approved drugs are the most common cause of **acute liver failure** in the United States*
--- by far

(We are not talking about chronic diseases that eventually lead to liver failure)

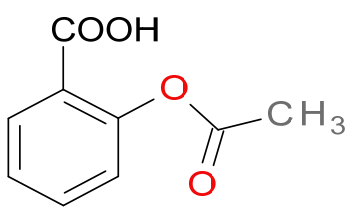
Etiology of ALF in the USA

Adult Registry (N=1,696) – courtesy W. Lee, M.D.

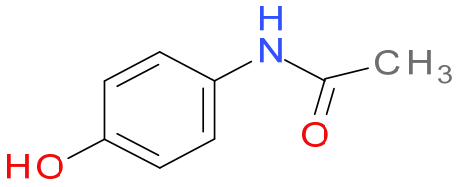


Why So Much Trouble with Acetaminophen ?

(a.k.a. "APAP" = N-acetyl-p-aminophenol {Lee}, paracetamol {England}, TYLENOL {trade})?



acetylsalicylic acid (ASA)
Gerhardt 1853; Bayer 1879
Dreser "aspirin" 1899



N-acetyl-p-aminophenol - "APAP"
or acetaminophen (Tylenol)

Because of its very successful McNeil-J&J marketing in the U.S. following the 1986 scare about use of aspirin in children with "flu" symptoms causing Reye's syndrome, sold widely as the "safe" aspirin

--- but the diagnosis of cause is difficult to make, so “indeterminate” as a cause is second to acetaminophen (APAP) overdose

We shall focus on the issue of causality as we develop this presentation, and tell you why

What is a "Hepatotoxic Drug"?

… an oxymoron: if the substance is truly and consistently hepatotoxic , it is <u>not</u> a drug

Admittedly some drugs are more likely to cause liver injury than others --- but some patients are more susceptible to the same drug and dose than are most people. Drugs are not intended to cause harm.

Drugs that Cause ALF

Rates of mild transient liver injury & ALF

	Incidence	
	ALT > 3X ULN	*ALF*
Isoniazid	**~ 10%**	**< 0.1%**
Troglitazone	**~ 2%**	**< 0.05%**
Ximelegatran	**~ 8%**	**< 0.05%**

Regulatory Actions due to DILI

Marketed Drugs: 1995-2009

Withdrawals

bromfenac

troglitazone

pemoline

ximelegatran*non-US

lumaricoxib*non-US

Special Use

trovofloxacin

felbamate

tolcapone

Warnings

acetaminophen

nefazodone

pyrazinamide/rifampin

valproic acid

atomoxetine

saquinavir

bosentan

erlotinib

(kava)

leflunomide

nevirapine

terbinafine

zifirlukast

interferon 1b/1a

infliximab

telithromycin

natalizumab

(lipokinetix)

Idiosyncratic DILI: Some Inciting Drugs

Hepatocellular injury, immunoallergic: **phenytoin, sulfonamides, allopurinol, halothane, diclofenac, quinolones, telithromycin,**

Hepatocellular injury, metabolic: **INH, troglitazone, ximelagatran, bromfenac**

Cholestatic**: estrogens, 17a androgens, chorpromazine, clavulinic acid, piroxicam**

Bile duct injury**: carbamazepine, chorpromazine, chlorpropramide, cyproheptadine, thiabendazole, haloperidol**

Microvescicular steatosis: ***valproate, tetracycline, didanosine***

Phospholipidosis & pseudoalcoholic hepatitis: ***amiodarone, perhexiline maleate***

Chronic autoimmune-like hepatitis**: dantrolene, methyldopa, nifurantoin, oxyphenisatin, propylthiouracil, tienilic acid**

What Do We Need to Know about DILI?

1. *How severe is it? In terms of function loss.*
2. *How probable is it that it was caused by the drug?*

Severity CANNOT be assessed by the level of serum enzyme elevation; that may indicate rate of hepatocellular injury but does not measure the ability of the liver to function and support life. The only true function tests often done are serum bilirubin and plasma prothrombin time.

Causality is another matter – very difficult

Serum Enzymes are NOT Liver *Function* Tests !

It is NOT a true function of the liver to regulate levels of enzyme activity in the plasma. Elevated levels may reflect injury to liver cells if injured but ***function*** must be measured by other tests.

The only tests commonly done that measure a true function of the liver are:

bilirubin concentration

prothrombin time, or its INR derivative

Don't call serum enzymes "LFTs", just say LTs.

Levels of DILI Severity

5	Death or Tx
4	Acute Liver Failure
3	Serious: Disabled, Hospitalized
2	Hy's Case: Injury with Slight Functional Loss
1	Serum Enzyme Elevations Only; Many People Adapt
0	No Adverse Effects Seen - Most People Tolerate Exposure

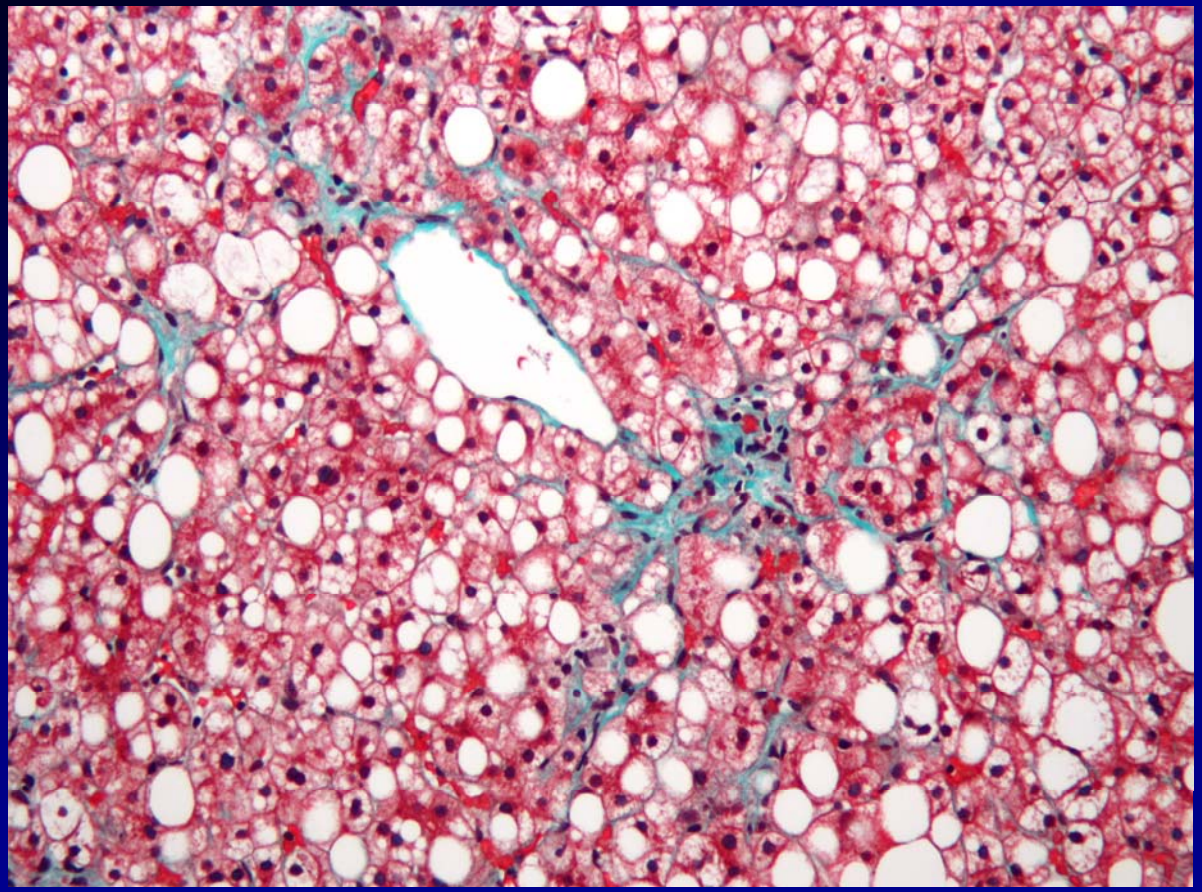
Likelihood That the Liver Problem was Caused by DILI

NCI/ FDA			DILIN
1	5 to 25%	“unlikely”	5
2	>25 to 50%	“possible”	4
3	>50 to 75%	“probable”	3
4	>75 to 95%	“very likely”	2
5	>95%:	“certain, definite”	1

Conversion: 6-FDA/NCI = DILIN

DILI Likelihood	Severity of Liver Dysfunction					
	5 fatal or transplant	4 acute liver failure	3 serious:	2 "Hy's case"	1 enzyme rises only	0 none detectable
5: definite *>95% likely*	25	20	15	10	5	0
4: very likely *>75 to 95% likely*	20	16	12	8	4	0
3: probable *>50 to 75% likely*	15	12	9	6	3	0
2: possible *>25 to 50% likely*	10	8	6	4	2	0
1: unlikely *5 to 25% likely**	5	4	3	2	1	0
0: certainly not *<5% likely***	0	0	0	0	0	0

… and some other cause very likely ;** *… and another cause almost certain, definite**



Hy Zimmerman
1916 - 1999

What is “Hy’s Law”?

- Hyman Zimmerman in 1968, 1978, and 1999 said that:

  “**drug-induced hepatocellar jaundice** is a serious lesion, with mortality from 10 to 50%” … *he did not say it was a law and didn’t want it named for him*

- Bob Temple articulated in 1999 a modified form of this observation for use in controlled clinical trials and dubbed it “Hy’s Law.”
  - {ALT or AST >3x upper limit of normal **AND** TBL> 2xULN}
  - Not primarily cholestatic; not caused by disease but by drug

It was catchy and now seems impossible to change

What “Hy’s Law” is NOT!

- Not just abnormal serum chemistries: ALT>3xULN & TBL >2xULN --- but they signal need to look closer
- Should not be initially cholestatic: ALTx / ALPx <2
- Must not be probably caused by other than drug --- find out
- Requires clinical adjudication (differential diagnosis) to determine probable cause of liver test abnormalities
- Often misunderstood by sponsors and their staffs, even by their consultants
- Important to find the probable cause of liver dysfunction

Identifying a DILI Signal
Clinical Trial Studies

Finding liver injury associated with exposure to a drug may indicate a higher risk to others exposed to the same drug –

(note: "associated with" or "related to" does not prove "caused by")

1 – Look for imbalance of liver injuries (enzyme rises) in randomized trials: more frequent and severe in those on drug

2 - Hy's case: ALT > 3 X ULN → bilirubin > 2 X ULN, not cholestatic and probably caused by drug: If present, predicts that serious idiosyncratic DILI cases may be more likely in post-marketing treatment population

FDA Experience

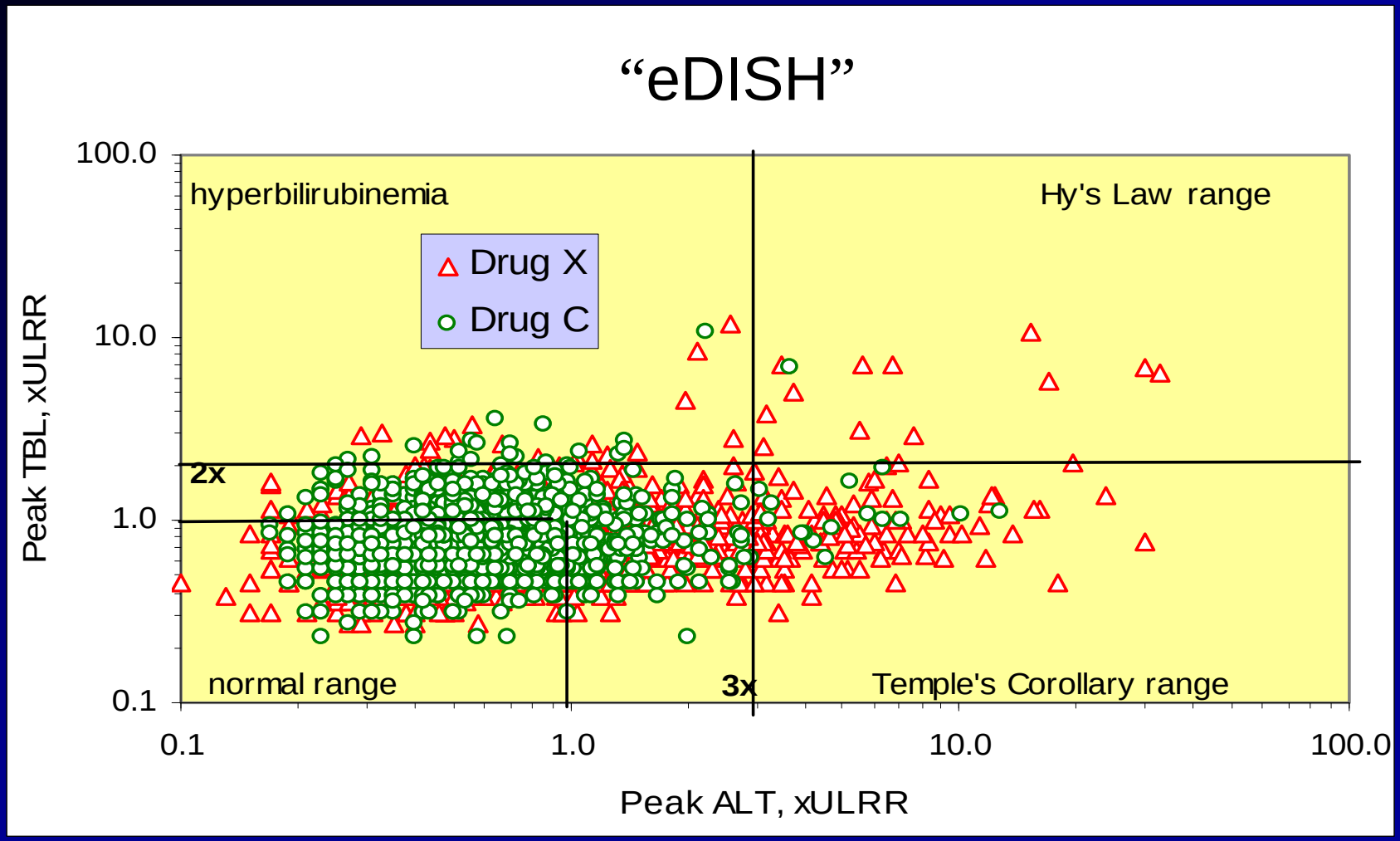
- Limitations of clinical trials
  - Subjects treated in a monitored setting
  - Have the disease being tested, nothing else
  - Selected participants, exclusion criteria
  - Limited numbers, limited time
- After product approval . . .
  - Often used off label, without monitoring, in patients different from those studied in the clinical trial, only voluntary reporting, burden on FDA to prove danger, huge numbers exposed

*The FDA Reviewers' Helper --- **eDISH***

--- an analytical tool, software program

(**e**valuation of **D**rug-**I**nduced **S**erious **H**epatotoxicity)

… to quickly find the needles in the haystack (rare subjects of special interest), for large controlled clinical studies … the few patients or subjects who need to be looked at more closely


"eDISH"
100.0
10.0
1.0
0.1
Peak TBL, xULRR
hyperbilirubinemia
Hy's Law range
Drug X
Drug C
2x
normal range
3x
Temple's Corollary range
0.1
1.0
10.0
100.0
Peak ALT, xULRR

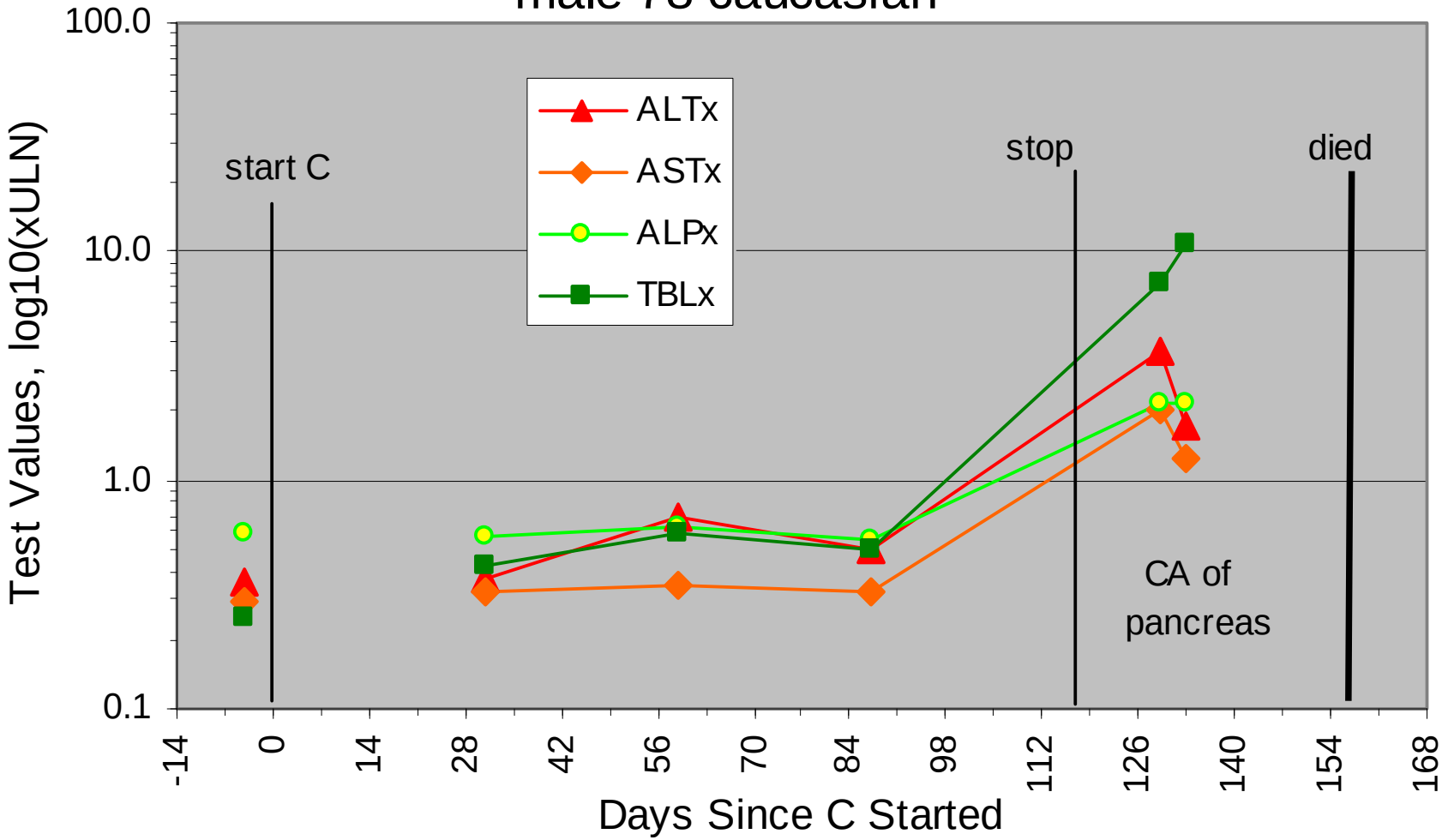
Treatment "C"

ID: 8675

Time Course of Liver Tests

C

male 78 caucasian



Subject #:8675, treatment: C, 78 yrs, white

Narrative:

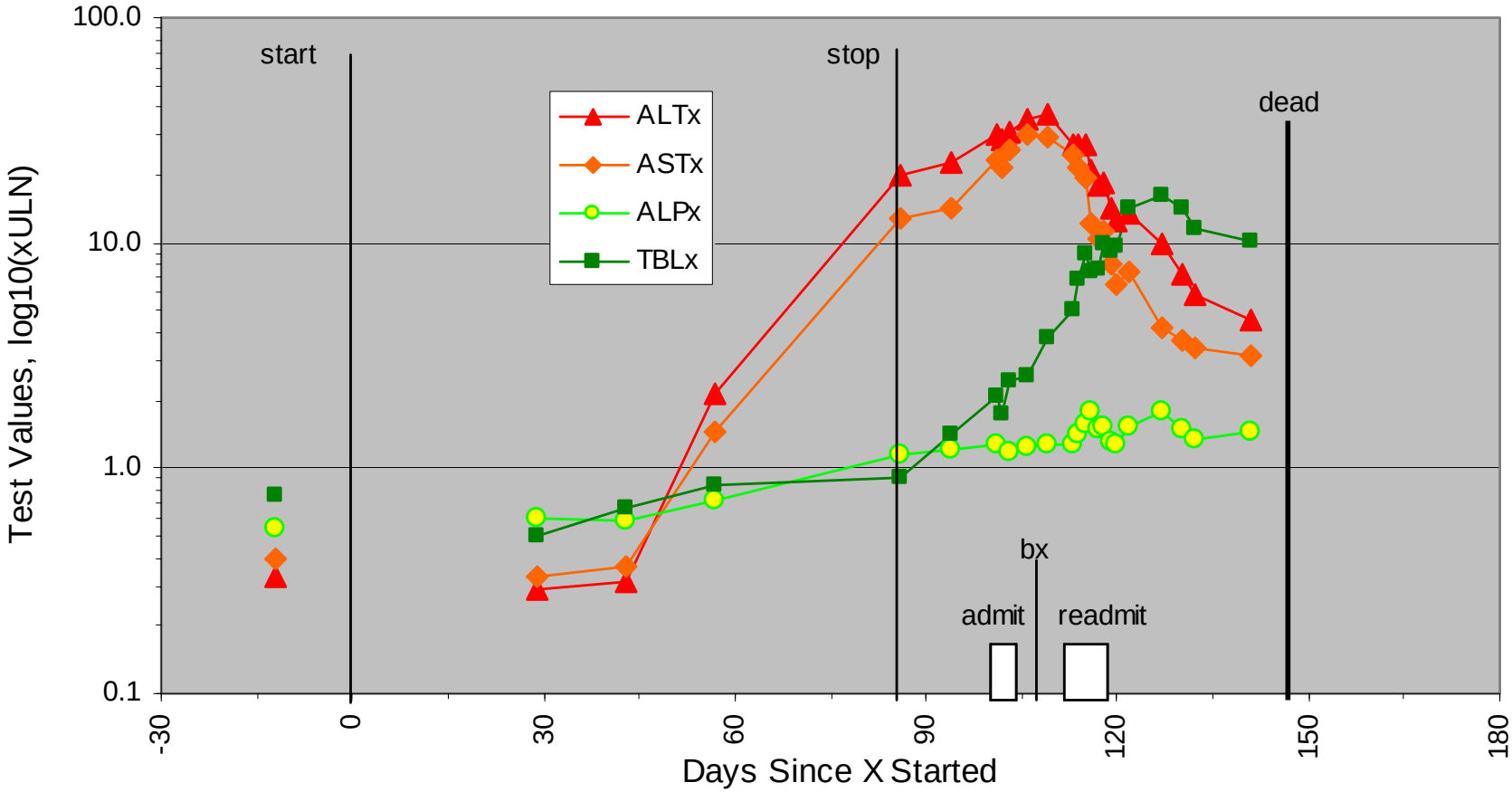
78-year-old white male, history of cholecystectomy, atrial fibrillation, hypertension, hyperlipidemia, coronary heart disease, congestive failure. Taking digoxin, pravastatin. Started Coumadin 13 Nov 2001, all tests (ALT, AST, ALP, TBL) normal before and for 3 months, but TBL, ALP and slight transaminase elevations noted March 2002. Stopped Coumadin 20 March. Abdominal mass found on CT, common bile duct occluded by tumor; bx = **pancreatic carcinoma**, not considered resectable. Patient died in hospice on 19 April 2002.

Treatment "X"
ID: 7259

X

Time Course of Test Values

male 80, caucasian



eDISH

In addition to the x-y log-log plot of peak ALT and TBL values for each person in the study, you then also need

The time course of all liver tests (ALT, AST, ALP, TBL) for patients or subjects of interest, and

- The clinical narrative, for clues to probable cause and severity of the liver dysfunction; differential diagnosis and should be written by a physician
- Try to determine the probable cause! Treat it.

Randomized Clinical Trials

- *Benefits*
  - Finding one or more true Hy's case alerts to possible serious DILI in larger future exposure population post-marketing
- *Limitations*
  - Selected population sample for inclusion in study
  - Insufficient powering for rare serious DILI events
  - Short duration of treatment may limit risk of seeing DILI
  - Isolated ALT increases not predictive of serious DILI

DILI Risk
Questions with Regulatory Impact

- Does a 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?

When Should We Ask These Questions?

At all phases of the drug's life cycle!

- Preclinical, before human exposure
- Clinical trials, leading to approval
- Post-marketing, after approval

People Differ in Their Responses

- No detected injury (‘tolerators’) - does not preclude micro-adaptive changes in liver cells
- Mild (transient & selective) injury (‘adaptors’) reflecting liver cell change followed by return to normal even if drug continued
- Clinically significant injury (‘susceptibles’) may be reversible when drug is withdrawn

Pattern and Extent of DILI

Patient 'Susceptibility' Factors

- Pre-existing conditions or diseases
- Age & Gender
- Nutritional status
- Alcohol (chronic vs acute)
- Concomitant drugs
- Genetic variants
- Multiple DILI phenotypes

Pattern and Extent of DILI

Patient 'Susceptibility' Factors

There are no "idiosyncratic drugs," only idiosyncratic recipients (whether people or animals)!

(idio = one's self + syn = together + crasy = mixing;

A person's unique particular mixing together of inherited traits and life experiences that may make his/her responses different than that of most others

Assessment of DILI Risk
--- *ask and find out:*

1. How many? population frequency
2. How much? severity of liver dysfunction
3. How soon? rapidity of onset, progression
4. How likely? probability of drug causation

CIOMS Diagnostic Scale *(RUCAM)*

*Roussel-Uclaf Causality Assessment Method**

Individual Criteria	*Range of Scores*
Time from start of Rx until event	+1 to +2
Time from stop of Rx until event	0 to +1
Course after stop of Rx	-2 to +3
Age	0 to +1
Alcohol/Pregnancy	0 to +1
Concomitant Rx	-3 to 0
Non drug-related causes	-3 to +2
Previous drug information	0 to +2
Dechallenge/Rechallenge	-2 to +3

Causality Assessment: Total Scores

If 8-10: highly probable: 6 or 7, probable; 3-5, possible; 1 or 2, unlikely.

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

The NIH DILI Network* (DILIN)

*Sponsored by NIDDK
http://dilin.dcri.duke.edu

Registries

Geographically/academically defined site-specific networks of inpatient/outpatient referral systems

- DILIN (US DILI); RRHSS (Spain DILI), SADRAC (Sweden DILI)
- ALFSG (US ALF network)
- UNOS (US liver transplant network)
- Vigibase (Europe)

- ***Benefits***
  - Registries for serious outcomes both in US & Europe
  - Structured clinical assessment of all patients referred for evaluation
  - Useful sampling of ‘what’s out there’
- ***Limitations***
  - Severe under-reporting
  - Poor content quality of reports

DILI Guidance *(July 2009)*
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
- guideline study *stop rules*
  - ALT/AST > 8x ULN or 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

Drug Life-Cycle Data Streams *DILI Risk Assessment* – Needs Improvement

- Randomized clinical trials – best data; too small/short
- AERS reports – usually inadequate data given
- Published case reports – spotty quality
- DILI in registries – often aimed at cost control
- Observational cohort studies – limited value
- Case-control studies – need confirmation

Summary

- Individual idiosyncratic susceptibility factors determine if subjects or patients exposed to a new drug will be '*tolerators*', '*adaptors*' or '*susceptibles*'
- In pre-approval clinical studies, milder injury may be important especially if function disturbed
- Post-market DILI risk assessment is more difficult to evaluate for severity and cause, mainly because of poor information, as well as under-reporting
- Predictive biomarkers of DILI that identify *susceptible patients* are needed but do not yet exist

Questions about DILI?

- E-mail: john.senior@fda.hhs.gov
  lana.pauls@ fda.hhs.gov
- http://www.FDA.gov *enter* **liver toxicity**

  into search window, click first entry, page down to see and review past annual meetings on topic