Positive Rechallenge Following Drug-induced Liver Injury

A review of 88 cases

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DR. SELIGMAN: Our final speaker of this session is Dr. Julie Papay from GSK. Dr. Papay.

DR. PAPAY: Let me just do a quick check on the audio. I think that's a bit better. I'd certainly like to thank John Senior as well as Lana Pauls for the opportunity to present this information on positive drug rechallenge.

This was an analysis done by a group of us, and I would like to recognize my colleagues who are in the audience who helped support this analysis. Dawn Clines, Susan Britt, Nancy Yuen and Chris Hunt, who were able to make it here today as well as Rezvan Rafi, who unfortunately couldn't be here.

Positive Rechallenge Following Drug-induced Liver Injury

- **Methods**
- Results
- FDA Guidance
- Conclusion

What I'd like to talk to you today is about positive drug rechallenge following drug-induced liver injury, a review of 88 cases. In the time allotted, I'd like to tell you a little bit about what we did, what we found, how our analysis complements the draft FDA Guidance and end with some concluding remarks.

Adjudication Criteria: 648 Positive Rechallenge Cases

3 criteria:

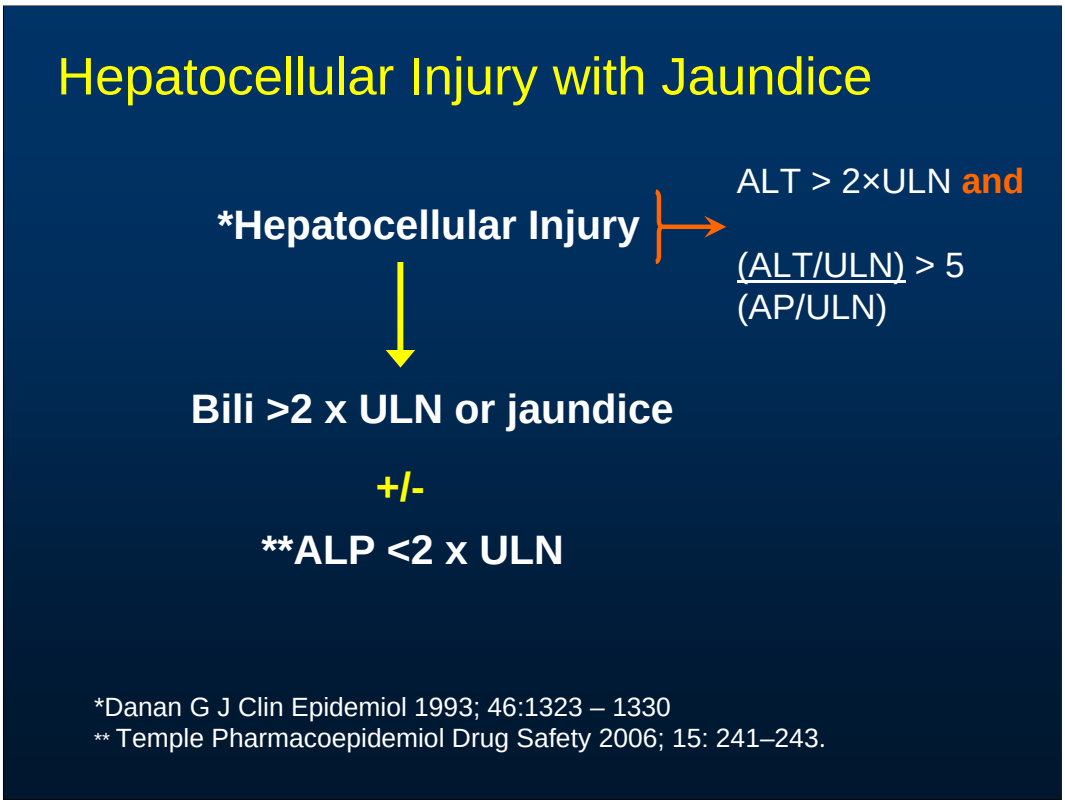
1. Initial hepatic event met RUCAM definition*:
   AST or ALT or Alk Phos >2xULN

2. ***AND*** positive dechallenge:
   liver chem. either normalized/resolved &/or >50% change from peak LFT/bilirubin within one month

3. ***AND*** a documented restart of medication (≥1 dose) +/- subsequent worsening of liver event met RUCAM definition*:
   AST or ALT or Alk Phos >2xULN

*Danan G J Clin Epidemiol 1993; 46: 1323 1330

A positive drug rechallenge was defined using the following three criteria. First, the case had to demonstrate an initial hepatic event that met the RUCAM definition published by Danan, et al., an internationally recognized criteria of an AST, ALT or alkaline phosphatase of greater than two times upper limit of normal. Second, the cases had to show a clear positive rechallenge to rule out chronic liver disease, and that was defined by liver chemistries that either normalized or resolved and/or had a greater than 50 percent change from peak LFT or bilirubin within one month. And finally, all cases in this analysis had to show a documented restart of medication of at least one dose with or without subsequent worsening of a liver event, that once again met the RUCAM definition of elevated AST, ALT or alkaline phosphatase greater than two times the upper limit of normal.



Cases were also evaluated for hepatocellular injury with jaundice better known as Hy's Rule, Hy's Law, Hy's Hypothesis, but originally identified by Dr. Hy Zimmerman. It's a hepatocellular injury defined as an ALT greater than two times the upper limit of normal with a ratio of ALT to alkaline phosphatase of greater than five, with concomitant bilirubin elevations of at least two times upper limit of normal or overt jaundice.

Causality Criteria: 648 Positive Rechallenge Cases

- 1991 Causality Classification in Pharmacovigilance in the European Community, from the CPMP Working Party on Pharmacovigilance
- Only cases possibly or probably related to suspect drug were included:
  - Probable “A” Reports including good reason and sufficient documentation to assume a causal relationship, in the sense of plausible, conceivable, likely but not necessarily highly probable.
  - Possible “B” Reports containing sufficient information to accept the possibility of a causal relationship, in the sense of not impossible or not unlikely, although the connection is uncertain or doubtful, for example because of missing data or insufficient evidence
  - Unclassified “O” Reports where causality is, for one reason or another, not assessable e.g., because of insufficient evidence, conflicting data, or poor documentation.

Meyboom RHB Pharmacoepidemiol Drug Safety 1992;1:87-97

In addition, cases were evaluated for alkaline phosphatase, whether or not it met a normal threshold. All cases were also evaluated using the causality score defined by the 1991 Causality Classification in Pharmacovigilance. Only cases that were possibly or probably drug related were included in this analysis.

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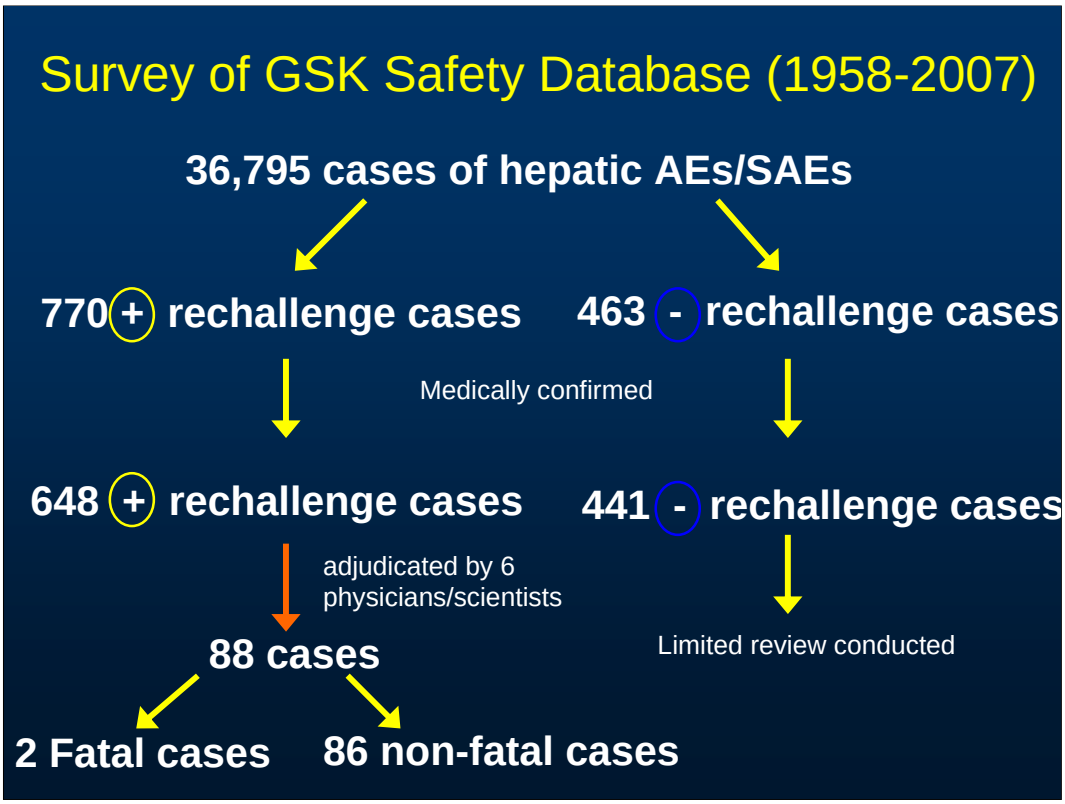
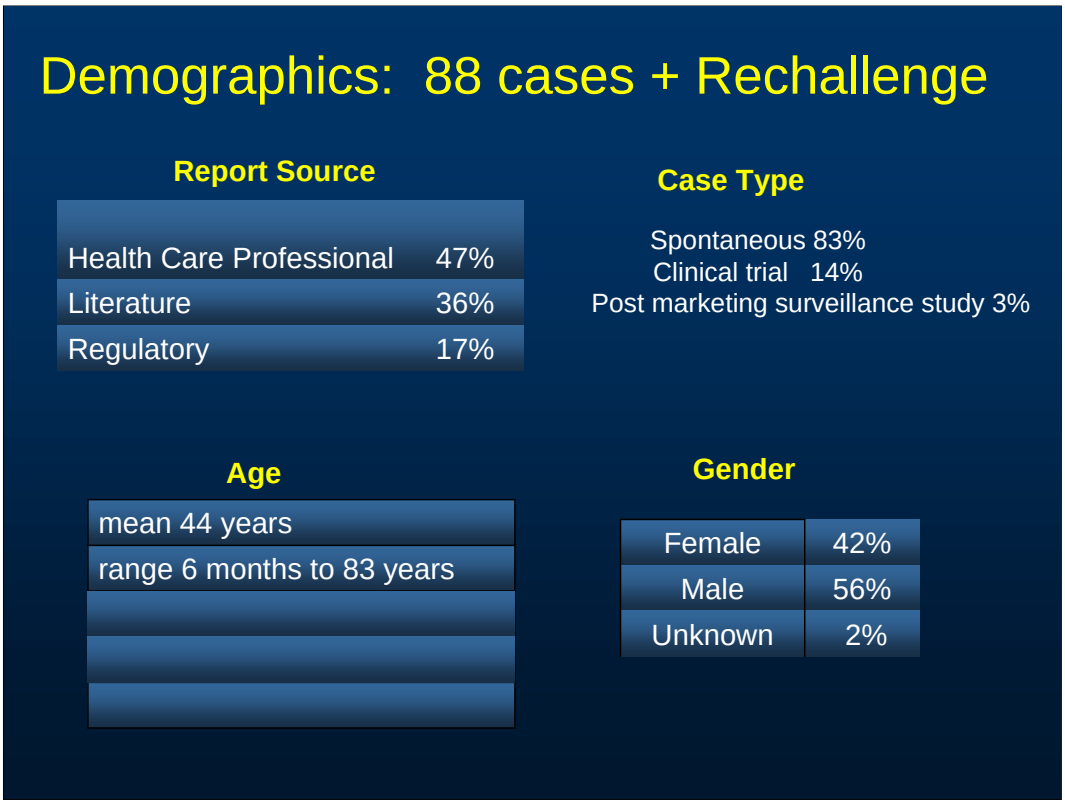
In other words, any reports that were considered unclassified, in which there was an inadequate amount of information, insufficient data or conflicting data, were not included in this analysis.



So to tell you a little bit about what we found, what I'd like to do is focus your attention on the left-hand side of the screen first. This analysis represents a survey of the GSK safety database which spans nearly 50 years of data. It is an international database of several merged PhRMA companies.

In our analysis, over 36,000 cases of hepatic adverse events and/or serious adverse events were identified including 770 positive rechallenge cases. Only those cases that were medically confirmed or reported by a regulatory agency were considered in this analysis. The majority of the cases were medically confirmed at 648, and this is where the real work came in, and this is where my colleagues helped out immensely. We had a team of six physicians and scientists who adjudicated 648 cases for all of the criteria that were discussed previously for positive rechallenge which resulted in 88 cases, 2 of which were fatal. So that's the positive rechallenge data set.

In addition, we did a limited review on negative rechallenge cases which is to the right of the screen. There were 463 cases that were identified in the database as negative rechallenge of which 441 were medically confirmed or reported by a regulatory agency, and a limited review was conducted on this data set.



But for the remainder of the talk, for the next few slides, I'd like to focus on the 88 cases of positive rechallenge that met rigorous criteria. The majority of these cases were reported by healthcare professionals, 47 percent. Of note, a third, over a third, 36 percent were reported in the literature and 17 percent were reported by regulatory agencies.

Surprisingly, this data subset was represented by a relatively young patient population at 44 years of age, although the range was fairly wide, 6 months to 83 years. When we look at the age breakouts, namely those patients who were over 55 years of age who were thought to be at increased risk of drug-induced liver injury, that represented almost a third of the data set but the vast majority were adults between the ages of 20 and 55 years.

In terms of who was reporting these positive drug rechallenges, most of the cases were reported spontaneously, 83 percent, although we did have 12 cases that were reported during our clinical trials of which half were the HIV portfolio. There were more men surprisingly in this data set of 56 percent versus women.

Outcome: 88 cases + Rechallenge

- 73% SAEs
- 2 fatal rechallenges probably related to suspect drug:
  - 62 year old female with CHF received troglitazone and up to 16 concomitant medications. She developed acute liver failure and multisystem failure with rechallenge 15 days after first liver event*
  - 83 year old male with CHF receiving paroxetine and 6 concomitant medications developed acute liver failure with rechallenge 17 days after first liver event**

*HC damage on rechallenge only (bili 2.62 mg/dL); normal AP

**HC damage + jaundice on rechallenge only; normal AP

To characterize this data set a little bit further, 73 percent met the FDA criteria for serious adverse events, that is they either resulted in a fatality, required hospitalization or were life threatening. This included two fatal rechallenges that were probably related to the drug. Both of these fatalities occurred in elderly patients who interestingly enough had congestive heart failure.

The first case occurred in a 62-year-old female with congestive heart failure who received troglitazone and multiple medications, up to 16 concomitant medications. She unfortunately developed acute liver failure and multisystem failure with rechallenge 15 days after the liver event.

The second fatality occurred in an 83-year-old male who received paroxetine and 6 concomitant medications. He also developed acute liver failure with rechallenge 17 days after the first event.

Drug Class in 88 Cases of Positive Rechallenge	Number of cases
Antibiotics (half are Augmentin)	21 (24%)
HIV meds (majority are NRTIs AZT, lamivudine, stavudine, abacavir, ddi)	13 (15%)
Azathioprine	14 (16%)
H2 antagonists (majority are ranitidine)	9 (10%)
5-HT3 antagonists (ondansetron/granisetron)	7 (8%)
Oncology meds (mercaptopurine, chlorambucil, pazopanib)	7 (8%)
Antidepressants (bupropion, paroxetine, tranylcypromine)	4 (5%)
Albendazole	3 (3%)
Antiviral – acyclovir, valaciclovir	2 (2%)
Cardiac meds (labetalol, carvedilol)	2 (2%)
Diabetic drugs (troglitazone, rosiglitazone)	3 (3%)
Allopurinol	1 (1%)
Phentermine	1 (1%)
Tranilast (for asthma)	1 (1%)
Total	88

What drugs were represented? Well, there was a broad class of drugs that we found in our data set. The majority of drugs fell into either the antibiotic class, half of which were amoxicillin-clavulanic acid and HIV medications. The largest set were represented by nucleoside reverse transcriptase inhibitors. Other drugs that were found in this data set include azathioprine, the H2 antagonists, 5-HT3 blockers and oncology medications. But as you can see there were a wide variety of medications that were found in this rechallenged analysis.

88 Positive Rechallenge Cases

Symptoms
Yes = 37 No = 15

PMH for liver disease
Yes = 15 No = 56

Type of Liver Injury
HC 51%, Cholestatic 24%, Mixed 10%, unknown 15%

Autoantibodies
Neg in 5 cases; +2 ANA in one

Concomitant Medications (n=69)

None recorded	18%
1 Med	20%
2 Med	14%
3 Med	14%
≥4 Meds	34%

When symptoms were reported, the majority of patients described some symptoms of hepatitis or jaundice, over 70 percent. However, the majority of patients did not have a past medical history for liver disease.

The type of injury was overwhelmingly hepatocellular, 51 percent followed by cholestatic and mixed disease, and very rarely autoantibodies were reported. Six cases actually documented that autoantibodies were measured, and they were negative in five case. Only one case reported amoxicillin-clavulanic acid demonstrated positive 2 ANA.

Many patients were receiving multiple medications, and I think of note what's impressive to me is the fact that 34 percent received more than 4 medications concurrently.

Time to Rechallenge

52% were rechallenged with same drug within one month

Timeframe	Number of cases
1 week (0-7 days)	6
2 weeks (8-14 days)	9
3 weeks (15-21 days)	16
4 weeks (22-30 days)	15
2 months (31-60 days)	10
3 months (61-90 days)	7
4 months	3
5 months	2
6 months	2
9 months	1
1 year	2
1-2 years	1
Unknown	14

All 3 cases were amoxicillin + clavulanate

Most of the rechallenges were inadvertent and over half of the patients were rechallenged with the same drug within one month. There were three cases that were outliers that occurred at one to two years and all of these cases occurred with the antibiotic amoxicillin-clavulanate.

Time to Onset of Drug Induced Liver Injury

Event 1

Timeframe	Number of cases
1 week (0-7 days)	16
2 weeks (8-14 days)	12
3 weeks (15-21 days)	8
4 weeks (22-30 days)	9
2 months (31-60 days)	15
3 months (61-90 days)	8
4 months	1
5 months	1
9 months	1
10 months	1
1 year	2
1-2 years	2
Unknown	12

Rechallenge Event

Timeframe	Number of cases
1 week (0-7 days)	40
2 weeks (8-14 days)	11
3 weeks (15-21 days)	7
4 weeks (22-30 days)	5
2 months (31-60 days)	3
5 months	1
Unknown	21

Event 1: Mean 3 weeks (1d-18 mos)

Event 2: Mean 1 week (hrs 5 mos)

In terms of time to onset for the DILIN event, rechallenge, the time to onset with rechallenge occurred much more rapidly, a mean of one week versus the initial event a mean of three weeks. And in particular, I'd like to draw your attention to the fact that 40 of the cases, almost half of the data set, on rechallenge experienced drug-induced liver injury within 1 week.

Negative Rechallenge Cases (n=441)

- Limited negative rechallenge case review and comparison to positive rechallenge cases revealed:
  - Similar demographics
    - mean age 43 yrs; 56% male
  - Similar drugs
    - antiretrovirals & antibiotics constituted 40%
  - No factors evident to explain differing response

Now I'd like to transition and tell you a little bit about what we found with negative rechallenge cases. A limited review was conducted on the negative rechallenge cases to compare to the positive rechallenge data set, and overall the demographics were similar with a mean age of 43 years, more men than women. In terms of breaking out by age, there was a similar amount, about a quarter of the cases were over the age of 55 years. Similar drug classes were implicated with negative rechallenge, although the number 1 and number 2 spot were flipped for negative rechallenge. Antiretrovirals were number 1 and antibiotics were number 2 and constituted 40 percent of the data set.

We didn't see any evident risk factors to explain the differences between the positive and negative rechallenge.

Positive Rechallenge Event Summary (n=88)

- Most rechallenge events occurred within one month of initial drug induced liver injury, many within one week
- Most exhibited symptoms of jaundice or hepatitis, when data available (71%, 37/52)
- Most received multiple meds besides suspect drug (82%, 57/69)
- Few had underlying liver disease (21%, 15/71)
- Hepatocellular injury most common type of injury (51%)

- A limited review of negative rechallenge cases (n=441) revealed similar demographics, drugs, with no clear trends

So just to summarize the data that we've reviewed thus far, most rechallenge events occurred within one month of the initial injury and many occurred within one week. Seventy-one percent of patients reported signs or symptoms of hepatitis or jaundice when symptoms were reported. Most received multiple medications and few had underlying liver disease, with hepatocellular injury as the most predominant form of injury. And a limited review of negative rechallenged cases on the data set of 441, revealed similar demographics, drugs and no clear trends.

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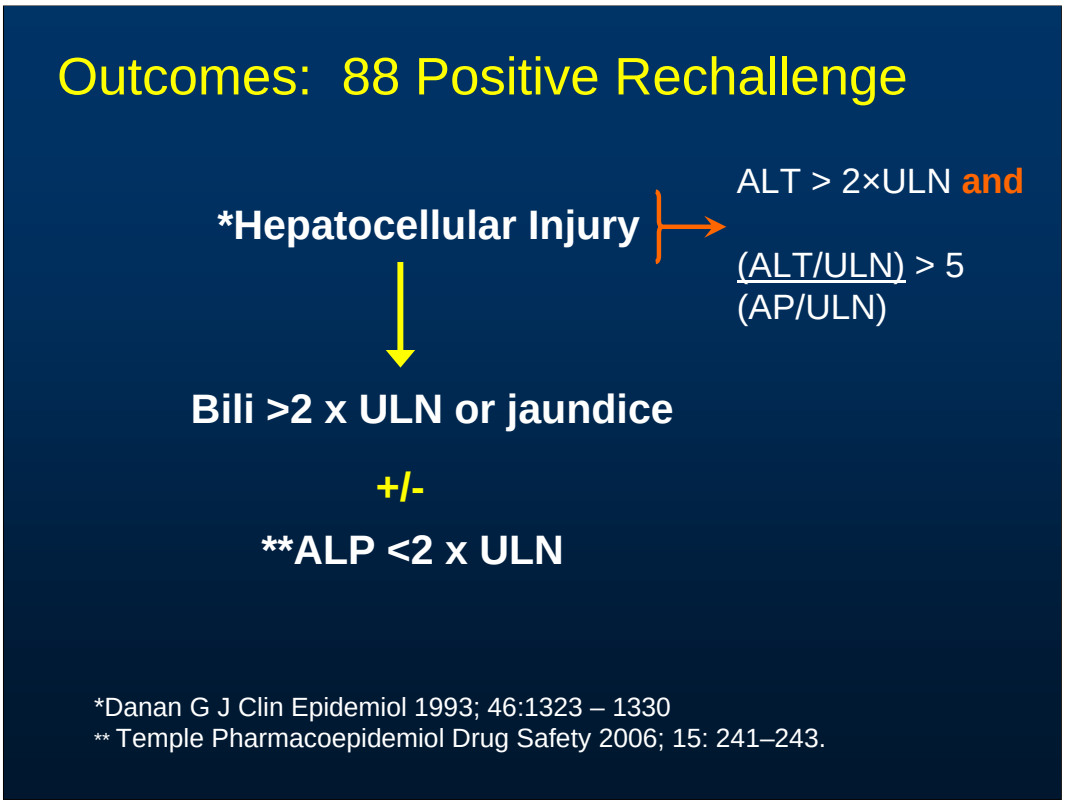
Let’s talk a bit about the outcomes.



I'm showing you this slide just to reorient you. I think most folks in the room are familiar with Hy's Law but these cases were also evaluated for evidence of hepatocellular injury with elevations in bilirubin with or without normal alkaline phosphatase which tells about biliary obstruction.

Outcomes (n=12)*: 88 + Rechallenge

Initial event only (n=3)	25%
Upon rechallenge only (n=2 fatalities)	17%
Both events (n=3)	25%
Jaundice described on rechallenge (n=4) (no labs provided for rechallenge)	33%

"Recurrent Hy's Law"

*including 8 cases (67%) with normal alk phos <2x ULN

Bilirubin >3 mg/dL in 11 of 12 cases

In the data set of positive rechallenge cases, 12 cases met Hy's Law. This included 11 cases that reported bilirubin that exceeded 3 milligrams per deciliter and I'd also like to note that 8 cases had normal alkaline phosphatase of less than 2 times upper limit of normal.

Cases Worse on Rechallenge (non-fatal): Recurrent Hy's law (n= 7)

Bilirubin & Transaminases on Initial Event & Rechallenge

Age/ Gender	Suspect Drugs	Time to Rechall	Outcome
58 Years/F	Azathioprine[1]	6 days	Improved
46 Year/M	Amoxicillin[2] trihydrate + potassium clavulanate	1 year	Hepatocell. hepatitis Resolved
*41 Years/M	Amoxicillin[3] trihydrate + potassium clavulanate	>23 months	Hepatocell. hepatitis Liver transplant

*Normal alk phos <2x ULN

[1]Sterneck M Hepatology 1991;14:806–810; [2] Breuskin F Acta Clinica Belgica 2001;56:255 257; [3]Andrade RJ Hepatology 2006; 44: 1581 1588.

The next few slides I'd like to focus your attention on seven cases that actually had recurrent Hy's Law, that is they had Hy's Law on the initial event followed by Hy's Law on rechallenge. This slide shows you 3 of the 7 cases that described increased bilirubin and transaminases on initial event and rechallenge, and this was represented by a case of a 58-year-old woman who received azathioprine. Fortunately, her Hy's Law case improved. This patient actually received azathioprine following liver transplant for chronic Hepatitis C infection. The other two cases received amoxicillin- clavulanate, one in a 46-year-old male, also whose drug-induced liver injury resolved. It also represents a 41-year-old male who unfortunately went on to liver transplant. All of these cases by the way are published in literature and the references are provided.

Cases Worse on Rechallenge (non-fatal; cont'd): Recurrent Hy's law (n= 7)

Jaundice Reported on Rechallenge Only

Age/Gender	Suspect Drugs	Time to Rechallenge	Outcome
*28 Years/M	Azathioprine[1]	30 days	Unknown
48 Years/F	Azathioprine[1]	Unknown	Unknown
49 Years/F	Azathioprine[1]	20 days	Unknown
*35 Years/M	Ondansetron HCl[2]	Unknown (probably <2 months)	Resolved

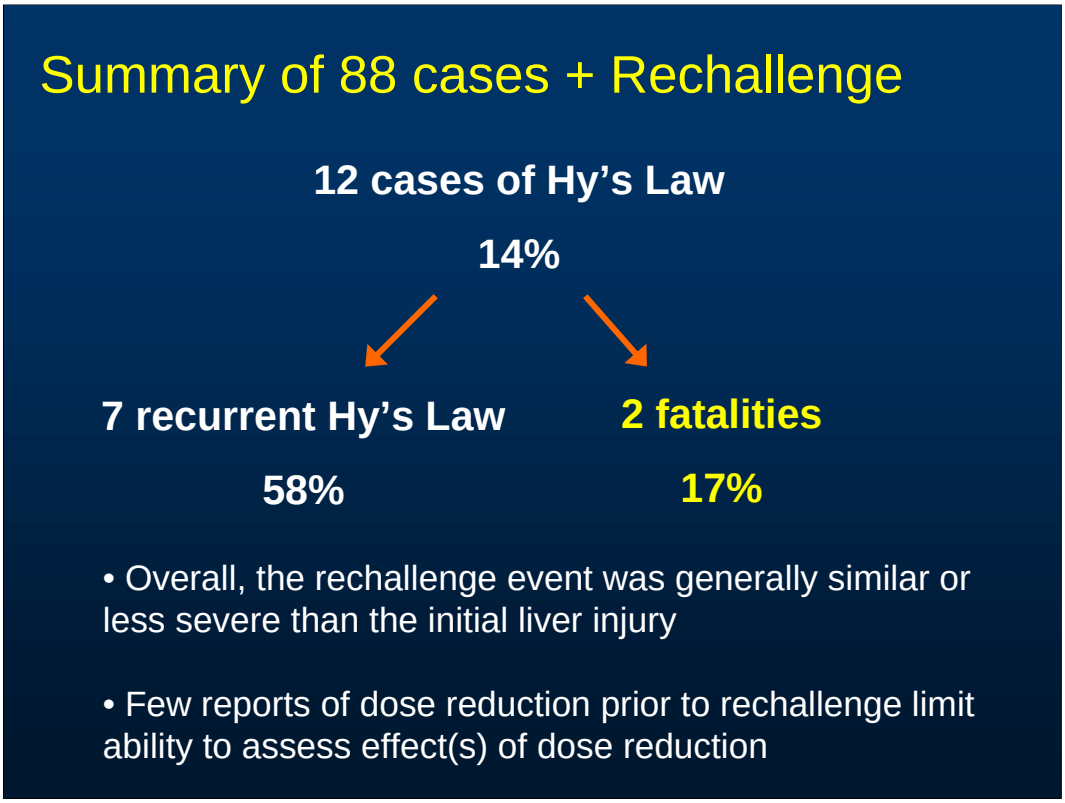
*Normal alk phos <2 xULN

[1]Ramahlo HJ Tranplantation Proceedings 1989;21:1716 1717

[2] Verrill M Lancet 1994;344:190-191

The remaining four cases that experienced recurrent on rechallenge of Hy's Law only reported jaundice but for completeness sake, that data is represented here. This includes three cases of azathioprine that were published by Ramahlo, et al. These patients received Azathioprine following renal transplant and of note, had normal liver function tests prior to transplantation.

The last case is an interesting case published by Verrill, et al., with ondansetron, and this patient was receiving IV doses of ondansetron prior to chemotherapy, received the first dose of IV ondansetron with chemotherapy, experienced elevations in LFTs and increased bilirubin, came in for a second course of chemotherapy and was again pretreated with ondansetron for chemotherapy-induced emesis, saw a recurrence of this event. With the third round of chemotherapy he was actually switched to granisetron, and there were no ill effects with respect to the liver.



So to summarize hepatocellular injury with jaundice, over half of the cases, 58 percent, actually experienced recurrence with rechallenge and this subset also included two fatalities

That said, overall the rechallenge event was generally similar or less severe than the initial injury in those cases that did not meet Hy's Law.

We did evaluate the effective dose and unfortunately there were just too few cases to evaluate for reducing the dose prior to rechallenge to note any trends or meaningful information.

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Comparison of select therapies:

Comparison of Select Therapies

Amoxicillin/clavulanate
Nucleoside reverse transcriptase inhibitors
Azathioprine
5HT antagonists
5HT3 antagonists

...these five drug classes represent over 80 percent of the drug classes that were observed with the 88 cases of positive rechallenge, and I'd like to talk to you a little bit about each of these in greater depth.

Possible Confounders in Select Therapies

NRTIs N=11	5 cases hepatitis C 3 alcohol use
Azathioprine N=14	1 liver transplant for hepatitis C
H2 antagonists N=9	1 case alcoholic liver disease 2 cases PMH drug allergy including one case with drug induced hepatitis with pyrazinamide/rash
5 HT3 antagonists n=7	1 case metastatic cancer with liver metastases 1 case h/o erythromyin-induced hepatitis 1 case (47 yo F) with positive EBV antibody

Confounders affected a minority of cases and occurred most frequently in HIV subjects receiving NRTIs

There were possible confounders with select therapies which included hepatitis C, past medical history for drug allergy, alcohol abuse, et cetera. However, most of the confounders affected the nuceloside reverse transcriptase inhibitor patients with HIV.

Amoxicillin/clavulanic acid (n=10)

Demographics:

- Mean age 50 years (40-78 years)
- 6 female; 4 male

- Presentation: 90% (9/10) developed jaundice after 1-4 wks; usually post-treatment
- Rechallenge cases similar to data published by Lucena et al.[1]

[1]Lucena Hepatology 2006;44:850 856.

In terms of what was found with the 10 case of amoxicillin-clavulanic acid, the mean age was 50 years. All of these cases represented adult patients. Six males and four females were represented in this data set. And, 90 percent involved jaundice after 1 to 4 weeks of starting their antibiotic. Usually these changes were seen a few days after finishing their antibiotic regimen.

Amoxicillin/clavulanic acid (n=10)

- 20% (2/10) met Hy's Law on initial event and rechallenge
- ALT more rapid with rechallenge, with mean drug duration:
  - 20 days to initial event
  - 4 days to rechallenge
- Liver chemistry grade[1] on rechallenge vs initial event:

  n=4 unchanged, n=1 increased, n=2 decreased, n=3 unknown

[1]DAIDs AE Grading Table Dec 2004 available
http://www3.niaid.nih.gov/research/resources/DAIDSClinRsrch/PDF/Safety/DAIDSAEGradingTable.pdf

And the information that we found in our data set is similar to the Spanish registry published by the Lucena, et al., who reported that in patients over the age of 55, there were higher elevations of bilirubin. Our data set corroborates that information in that patients who were over the age of 55 had an average bilirubin elevation of 14 milligrams per deciliter, versus younger patients, less than 55, only had bilirubin elevations of about 7 milligrams per deciliter. So very similar data.

In addition, two of the cases met Hy's Law on the initial event and rechallenge. The rises in ALT were much more rapid on rechallenge than the initial event, with 4 days versus 20 days and when you look at the Division of AIDS, liver AE grading tables, we wanted to see how bad were the elevations on rechallenge or did you tend to see some adaptation. Four cases, their DAIDS grade scoring remained unchanged, one increased, two decreased and three didn't provide enough information to make an assessment.

Nucleoside Reverse Transcriptase Inhibitors (n=11)

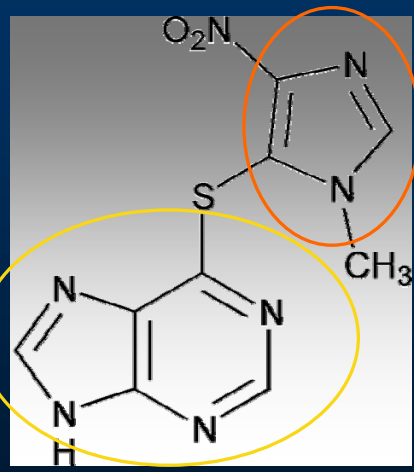
- Median age 41 (6 mos - 57 years), 9 male/1 female/1 unk
- Most events asymptomatic (jaundice in two cases)
- No Hy's Law cases
- Mean duration of drug therapy to first event: 2.6 months
- Liver injury frequently hepatocellular:
  - 55% hepatocellular (abacavir)
  - 27% cholestatic (zidovudine/lamivudine)
  - 18% unassessable
- Liver chemistry grade[1] on rechallenge vs initial DILI:
  n=6 unchanged, n 1 increased, n=3 decreased, n=1 unknown

[1]DAIDs AE Grading Table Dec 2004

In contrast, with the NRTIs most of the liver injury was hepatocellular in nature, and many of these cases had asymptomatic elevations in their ALTs that occurred months after starting therapy. So a very different picture than amoxicillin-clavulanate. The mean age was 41 years although there was a broad range. One case reported exposure in a six-month old. There were no Hy's Law cases in this subset and liver chemistry grade on rechallenge versus the initial, six remained unchanged, one increased and three decreased.

Azathioprine n=14

- Mean age 46 years (21-63);
  9 male/5 female
- Presentation:
  - 57% (8/14) developed asymptomatic ↑ LFTs
  - 43% (6/14) developed jaundice that reappeared on rechallenge
- Liver injury usually hepatocellular:
  - 71% hepatocellular
  - 21% cholestatic
  - 7% mixed
- 2 cases w/eosinophilic portal infiltrate on bx
- 29% (4/14) met Hy's law on initial injury & rechallenge[1,2]
- ALT more rapid with rechallenge, with mean drug duration:
  - 3 months to initial event
  - 10 days to rechallenge event



[1]Sterneck M Hepatology 1991;14:806–810;
[2]Ramahlo HJ Tranplantation Proceedings 1989;21:1716-1717

In the interest of time, I'll quickly go through the next three data sets, but suffice it to say that for azathioprine, the 5HT3 antagonists and H2 blockers, the form of liver injury was hepatocellular in nature, had a quicker time to onset after rechallenge than the initial event and azathioprine, like the NRTIs, typically the injury occurred months after starting the drug.

H2 Antagonists (n=7 ranitidine, 2 cimetidine)

- Mean age 49 years (40-78), 5 male/4 female
- Liver injury frequently hepatocellular:
  - 55% hepatocellular
  - 22% mixed
  - 22% unassessable
- 22% (2/9) met Hy's Law on *initial injury only*
- ALT more rapid with rechallenge, with mean drug duration:
  - 33 days to initial event
  - 7 days to rechallenge
- Liver chemistry grade[1] on rechallenge vs initial DILI:
  n=2 unchanged, n 1 increased, n=3 decreased, n=3 unknown

[1]DAIDs AE Grading Table Dec 2004; [2]Luparini RL Ann Ital Med Int 2000;15:214-217;
[3]Hiesse C Lancet 1985;1:1280

For H2 blockers, the form of liver injury was hepatocellular in nature, had a quicker time onset after rechallenge than the initial event and, typically the injury occurred months after starting the drug.

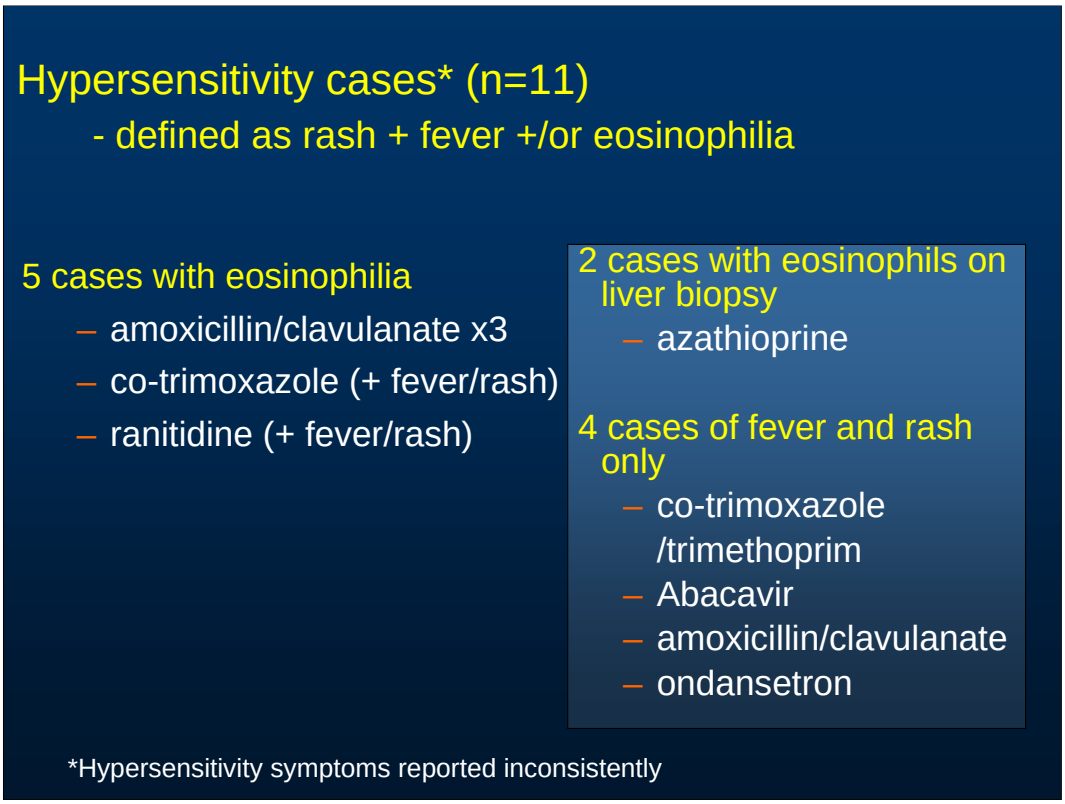
5HT3 Antagonists (n=6 ondansetron, 1 granisetron)

- Mean age 46 years (11-69), 3 male/4 female
- Liver injury usually hepatocellular:
  - 71% hepatocellular
  - 29% unassessable
- 1 case met Hy's law on initial injury & rechallenge[1]
- Liver chemistry grade[1] on rechallenge vs initial DILI:
  n=2 unchanged, n=4 decreased, n=1 unknown

[1]Verrill M Lancet 1994;344:190-191

[2]DAIDs AE Grading Table Dec 2004

With 5HT3 antagonists, the form of liver injury was hepatocellular in nature, had a quicker time onset after rechallenge than the initial event and typically the injury occurred months after starting the drug.



Just to stay on track with time, there has been a fair amount discussed about hypersensitivity and the role that might play in drug-induced liver injury. We evaluated cases for rash, fever and/or eosinophilia and five case were documented with eosinophilia including three with amoxicillin-clavulanate, one with cotrimoxazole and one with ranitidine. And I should pause and say here that out of all the data shown on this slide, there's only one case that occurred with amoxicillin-clavulanic acid in which the patient had eosinophilia and also met with Hy's Law.

In addition, there were two cases with eosinophilia infiltrates that were noted on the liver biopsy. Both of those cases occurred with azathioprine. None of those case met Hy's Law. And there were four cases of fever and rash reported only, and that included one case with abacavir hypersensitivity reaction.

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- **FDA Guidance**
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So how does this information complement the draft FDA Guidance, and I think it complements it quite well.

FDA Draft Guidance – Drug Induced Liver Injury

- Rechallenge should only be considered when:
  - ALT elevations do not exceed 5x ULN
  - a patient has shown clear therapeutic benefit from the drug & other options are not available OR
  - substantial accumulated data does not show potential for severe injury
  - requires subject consent & monitor closely

*FDA Draft Guidance. DILI Premarketing Clinical Evaluation. October 2007

The FDA draft Guidance suggests that rechallenge should only be considered when you see ALT elevations that do not exceed more than five times upper limit of normal and when a patient has shown a clear therapeutic benefit from the drug when other options are not available or you know there's enough data out there to suggest that the drug is not the likely offender. It obviously requires the patient understand the risk benefit and give consent before rechallenge.

ALT<5xULN in 16/88 rechallenge cases

- 13/16 cases: event no worse on rechallenge
- 3/16 cases: event similar/more severe on rechallenge; no fatalities
  - 61yoM with rheumatoid arthritis & azathioprine hypersensitivity hepatitis on liver biopsy with fever, chills, malaise, **jaundice**, cholestatic hepatitis with eosinophils on biopsy, and acute interstitial nephritis[1]
    - Concom. meds: naproxen (rapidly tapered)
  - 35yoM with neuroectodermal cancer with fever, **jaundice** with ondansetron initial and rechallenge liver events[2]
    - Concom. meds: ifosfamide, doxorubicin, vincristine, Mesna
  - 75yoM with chronic lymphocytic leukemia and hypothyroidism with hepatocellular injury on chlorambucil rechallenge exhibited doubling of ALT and AST in rechallenge event compared with initial event[3]
    - Concom. meds: prednisone, thyroxine
- Evidence base suggests that ALT≤5xULN without jaundice a better threshold for drug rechallenge after probable drug-induced liver injury

1. Meys J Rheumatol 1992;19(5):807, 2. Verrill Lancet 1994;344:190, 3. spontaneous report

So the first criterion, for ALT elevations that did not exceed five times upper limit of normal, we went back and reviewed our data set of 88 cases of positive rechallenge and we found that 13 of 16 cases that did not have worsening other than on rechallenge. However, there were 3 cases that did get worse on rechallenge who had ALTs less than five. Two of those patients reported concurrent jaundice with the ALT less than five and one patient, a 75-year-old male, who had leukemia who received chlorambucil experienced a doubling of the LFTs following the challenge.

Positive Rechallenge Following Drug-induced Liver Injury

- Methods
- Results
- FDA Guidance
- **Conclusion**

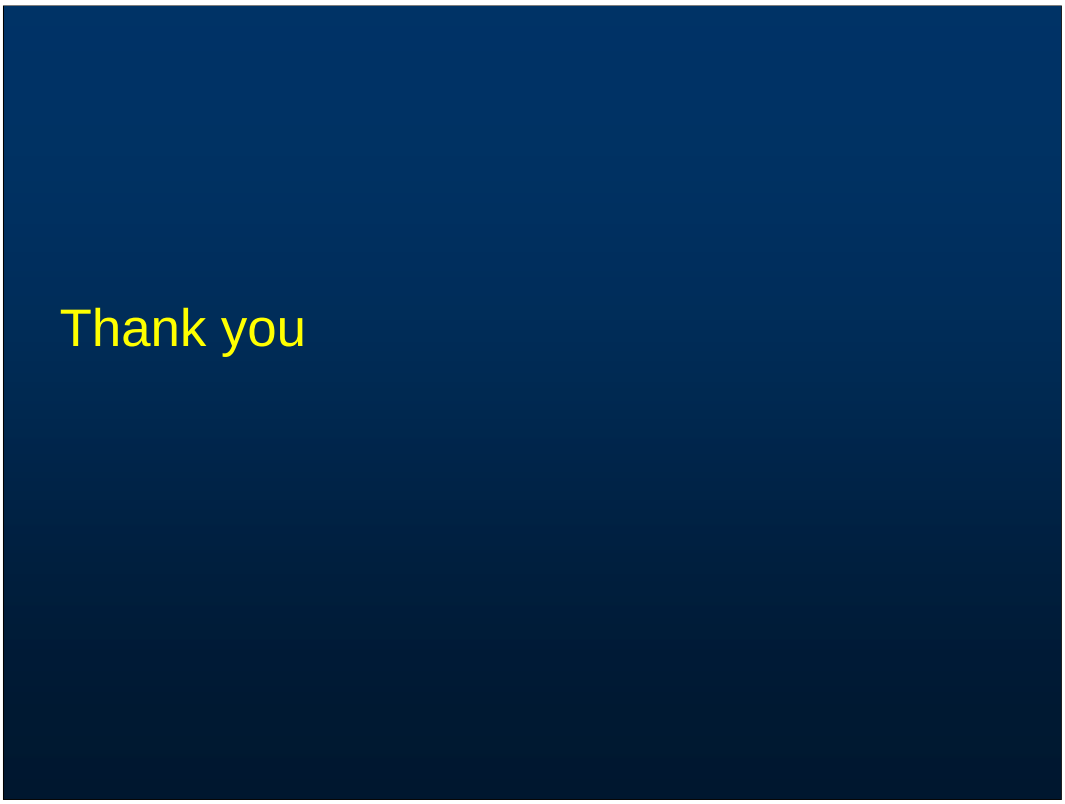
So I think it would complement the FDA Guidance quite nicely if inclusion of rechallenge might be considered in patients who have ALTs less than five times upper limit of normal without jaundice.

Conclusions

- Drug rechallenge following drug-induced liver injury may result in recurrence of adverse effects
- 2 fatalities, although HC injury occurred with initial event, HC injury with ↑ bilirubin (>2 mg/dL) only occurred on rechallenge
- The short time interval (<1mo) between initial drug-induced liver injury and rechallenge suggests that drug rechallenge could be prevented by:
  - improved recognition of drug-induced liver injury
  - HCP communication to patients (as per allergies)
  - improved health records

And just some concluding remarks, drug rechallenge following DILI may result in the recurrence of adverse effects. We had a fair number of recurrence of Hy's Law on rechallenge. Fatalities can happen and in our data set, the two fatalities, demonstrated Hy's Law upon rechallenge only. The initial liver injury was hepatocellular in nature and did not meet Hy's Law.

The short time interval, less than one month between the initial drug-induced liver injury and rechallenge, suggests that we can do a better job and prevent rechallenge first by improving the recognition of drug-induced liver injury from clinicians who are seeing patients as well as communicating to our patients that they had a potentially serious drug-induced liver injury with a drug, making sure that those patients understand that they've had the event and the name of the drug, not only the trade name but the generic name, perhaps even, you know, patients could wear a Medic Alert bracelet or carry a medication guide in their wallet because patients move, doctors change and unfortunately all health records are not electronic. And we can also do a better job of improving our health records. In our data set, inadvertent rechallenge was reported in one hospital on different floors.



So I think that there is learning that can be shared and improvement that can be made regarding drug-induced liver injury.

In conclusion, a heightened awareness is needed about positive rechallenge following drug-induced liver injury, given the potential for serious adverse events and sometimes fatal outcomes and in general, clinicians should avoid such rechallenges. Thank you.

(Applause.)