Patients with Underlying Liver Diseases:

Why Should We Continue to Exclude Them?

Arie Regev, M.D.
Global Patient Safety
Eli Lilly and Company

Hepatotoxicity Special Interest Group Meeting

Silver Spring, MD

DR. REGEV: Actually, John asked me to present the opposite opinion from what we heard in the last two sessions and that is: “Why should we actually continue to exclude those patients with underlying liver disease?

And for those of you who don't know me, I'm now with Eli Lilly, but before that I was a hepatologist in academic centers for about 13 years. In the last 9 years I have worked at the University of Miami. So I’m going to present this from the perspective of not only a pharmaceutical company, but also from a hepeatologist perspective.

Why Should We Include Subjects with Underlying Liver Diseases?

- "…they are likely to be treated with the drug if it is marketed."
- "If the drug is intended to be prescribed or marketed to such patients after approval, they should be studied during controlled trials."

Guidance for Industry. FDA. October 2007

We all know the advantages of including patients with underlying liver diseases in clinical studies, and they are listed in the in the FDA draft Guidance. These patients are likely to be treated with the drug after marketing, and if the drug is intended to be prescribed post-marketing, why not treat them in the clinical study setting?

Potential Problems

- DILI may worsen a coexisting acute liver disease
- DILI may lead to decompansation in patients with liver dysfunction
- ULD may increase incidence/severity of DILI
- ALT fluctuations due to underlying liver disease
  - May lead to early discontinuation of a study drug
  - May lead to early termination of the study
- Flare up of underlying liver disease due to the drug
- Flare up of alcoholic liver disease due to recurrent drinking
- Increase in fatty infiltration in NAFLD patients

Well, it is a nice concept in general, and I not argue with this, but I'm going to submit to you that there are a few problems with this concept.

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Let's take care first of the issues that we all agree on, starting with the fact that we're not going to give investigational drugs in a clinical study setting to patients with acute liver disease. I think we have complete agreement on that. So I'm going to just take it off the discussion. Patients with acute hepatitis A, even if they look just moderately sick, can be extremely sick if anything changes in the system; we know that from patients who had cholecystectomies during acute viral hepatitis, and they do very poorly.

And let's agree that we're not going to discuss the second point here, which is that we don't want to give experimental medications to patients with decompensated liver disease, and I think there's enough evidence to support this.

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So I'm going straight to the third issue, and here this had been discussed here yesterday several times. I think by now we can probably say that we have many examples where underlying liver disease can actually increase the severity or incidence of drug-induced liver disease.

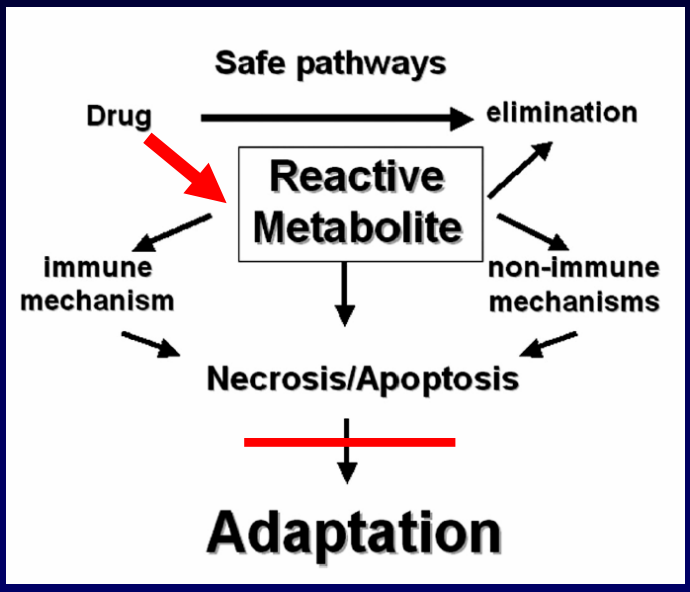
Could the Conventional Wisdom be Wrong?

"The often cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact"

Hyman Zimmerman

We mentioned many times that when Hyman Zimmerman had made his comments, there was little foundation in fact to this thought, but the factual foundation has increased in the last 10 years.

Increased Incidence of DILI in Patients with Underlying Liver Disease



Watkins. *Toxicologic Pathology; 2005*:33:1–5

I'm not going to discuss the mechanism here. I don't know if it is because the addition of a drug to a patient with an underlying liver disease actually increases the actual incidence of DILI or if it interferes with protective mechanisms such as adaptation. For all practical purposes, we will end up with a patient with severe drug-induced liver injury. So it doesn't really matter what is the mechanism.

Role of Underlying Liver Disease in Increasing Rate of DILI

HEPATOLOGY Vol. 31, No. 1, 2000

Antituberculosis Drug-Related Liver Dysfunction in Chronic Hepatitis B Infection

WAI-MAN WONG,[1] PUI-CHEE WU,[2] MAN-FUNG YUEN,[1] CHI-CHUNG CHENG,[1] WING-WAI YEW,[3] POON-CHUEN WONG,[3] CHEUK-MING TAM,[4] CHI-CHIU LEUNG,[4] AND CHING-LUNG LAI[1]

Liver toxicity is a common side effect of antituberculosis (anti-TB) drugs. We studied the differences in liver dysfunction observed during anti-TB treatment between hepatitis B virus carriers (HBV) and noncarriers. Three hundred twenty-four patients on anti-TB drugs were recruited and followed up for 1 year. Forty-three patients with HBV and 276 non-HBV patients were included for analysis. Liver function tests and viral markers were monitored monthly. Liver biopsy was requested whenever the alanine transaminase (ALT) was persistently abnormal. Eighty-six HBV carriers who were not given anti-TB drugs were chosen as a second control and evaluated prospectively. The incidence of liver dysfunction was significantly higher in HBV carriers given anti-TB drugs (34.9%) when compared to noncarriers (9.4%, $P < .001$) and with HBV carriers not given anti-TB drugs (8.1%, $P < .001$). For patients given anti-TB drugs, HBV carriers who developed liver dysfunction were younger ($P = .011$) and had more severe liver injury compared with noncarriers ($P = .008$). By multiple logistic regression analysis, age ($P = .002$) and hepatitis B infection ($P < .001$) were the only 2 significant risk factors for hepatotoxicity related to anti-TB therapy. (HEPATOLOGY 2000;31:201-206.)

And we have many examples of that. I'm going to bring very few because of time constraints. This is an article published in 2000 in Hepatology, showing the risk of hepatotoxicity from anti-TB drugs in patients who had an underlying hepatitis B. I'm just going to read this sentence: "The incidence of liver dysfunction was significantly higher in HBV carriers given anti-TB drugs. The incidence of DILI was 35 %t in HBV carriers compared to 9.4 % in non-carriers, and 8.1% in HBV carriers not given anti-TB drugs." So this liver dysfunction was induced by anti-TB medication. And the authors conclusions were that age and hepatitis B infection were the only two significant risk factors for hepatotoxicity related to anti-TB therapy. This is not new information. There is actually an earlier study showing the same thing with hepatitis C patients and anti-TB drugs.

Role of Underlying Liver Disease in Increasing Rate of DILI

AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE VOL 157 1998

Antituberculosis Drug-induced Hepatotoxicity

The Role of Hepatitis C Virus and the Human Immunodeficiency Virus

JAIME R. UNGO, DENIS JONES, DAVID ASHKIN, ELENA S. HOLLENDER, DAVID BERNSTEIN, ANTHONY P. ALBANESE, and ARTHUR E. PITCHENIK

The University of Miami School of Medicine, Division of Pulmonary Diseases and Critical Care Medicine, Division of Gastroenterology, Department of Internal Medicine, Miami; A. G. Holley State Hospital, Lantana; Addiction Treatment Program Mount Sinai Medical Center, Miami Beach; V. A. Medical Center, Miami; The Florida Bureau of Tuberculosis Control and Prevention, Tallahasse, Florida; The Division of Gastroenterology, Winthrop University Hospital, Mineola, New York

RELATIVE RISKS FOR DEVELOPING DRUG-INDUCED HEPATITIS

	Patients		DIH				
Viral Serologies	(*n*)	(%)	(*n*)	(%)	Relative Risk	95% Confidence Limits*	p Value†
HCV (−) HIV (−)	55	43	3	5	1	—	—
HCV (+) HIV (−)	29	23	7	24	5	1.305–23.311	0.028
HIV (+) HCV (−)	33	26	7	21	4	1.114–19.541	0.036
HIV (+) HCV (+)	11	9	5	45	14.44	2.740–76.135	0.002

As you can see in this study, patients who had hepatitis C with no HIV coinfection and received anti-TB drugs had five times more risk of developing drug-induced hepatitis. And by the way,coinfection with both HIV and HCV increased this risk by almost 15 times. So again this is well documented information, and I could bring you several other studies showing the same thing..

Role of Underlying Liver Disease in Increasing Rate of DILI

Table 1. Prospective studies on the effect of hepatitis C virus (HCV) and hepatitis B virus (HBV) coinfection on severe liver injury (defined as transaminase elevations) in patients with HIV infection who are receiving HAART.

Study [reference]	No. of subjects	Average CD4 cell count, cells/mm^3	Follow-up	Relative risk of hepatitis, by infection status: Positive[a]	Relative risk of hepatitis, by infection status: Negative	Grade 3 or 4 transaminase elevation used as end point	Other associations
Martinez et al. [14]	610	279	Every 3 months	2.5 (HCV)	1	Yes	Duration of therapy
Monforte et al. [15]	1255	327	Every 3 months	10.6 (HCV), 8.4 (HBV)	1	No	Zidovudine or zalcitabine therapy
Sulkowski et al. [1]	298	~200	Every 3 months	3.7[b]	1	Yes	—
Saves et al. [12]	1253	144	⩾1 test	3.2 (HCV), 3.0 (HBV)	1	No	—

- HCV coinfection is associated with a 2-10-fold increase in risk of developing elevated aminotransferase levels during HAART

M. Bonacini. CID 2004:38 (Suppl 2):S104-S108

The same thing was shown with other groups of drugs, such as anti-HIV drugs (or HAART) in patients with hepatitis B or C. As you can see in this review article, patients with underlying hepatitis C had 2.5, 10.6, 3.7, and 3.2 times higher risk of severe drug-induced liver injury due to anti-HIV drugs, compared to patients with no underlying hepatitis C

The authors concluded that coinfection with hepatitis C is associated with 2 to 10-fold increase in the risk of developing aminotransferase elevations during HAART therapy.

Role of Underlying Liver Disease in Increasing Rate of DILI

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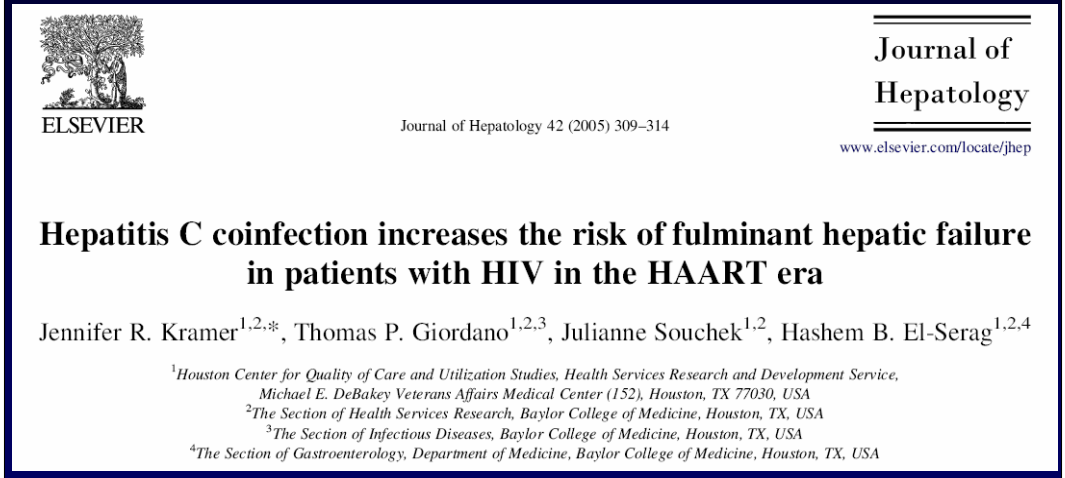
- HBV coinfection is associated with a 3-8-fold increase in risk of developing elevated aminotransferase levels during HAART

M. Bonacini. CID 2004:38 (Suppl 2):S104-S108

The same was found in patients with underlying hepatitis B, which was associated with 3 to 8-fold increase in the risk of DILI. We are always faced with the question: was it the drug that caused the liver injury, or was it the underlying liver disease?

Well, although it is not easy to differentiate between the two in some cases, it looks more and more like the drug is really the cause in many of these studies. This is nicely demonstrated in the next study.

Role of Underlying Liver Disease in Increasing Rate of DILI



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Journal of Hepatology 42 (2005) 309–314

Journal of Hepatology

www.elsevier.com/locate/jhep

Hepatitis C coinfection increases the risk of fulminant hepatic failure in patients with HIV in the HAART era

Jennifer R. Kramer[1,2,*], Thomas P. Giordano[1,2,3], Julianne Souchek[1,2], Hashem B. El-Serag[1,2,4]

[1]*Houston Center for Quality of Care and Utilization Studies, Health Services Research and Development Service, Michael E. DeBakey Veterans Affairs Medical Center (152), Houston, TX 77030, USA*
[2]*The Section of Health Services Research, Baylor College of Medicine, Houston, TX, USA*
[3]*The Section of Infectious Diseases, Baylor College of Medicine, Houston, TX, USA*
[4]*The Section of Gastroenterology, Department of Medicine, Baylor College of Medicine, Houston, TX, USA*

- A retrospective study using the Dept. of Veterans Affairs database
- 11,678 patients with HIV-only and 4,761 patients with coinfection

This study, published in the Journal of Hepatology 2005, examined the risk of fulminant hepatic failure in patients with HIV in the HAART era. This large study looked at 11,678 VA patients who were infected with HIV only, and at 4,761 coinfectied with HIV and HCV.

Role of Underlying Liver Disease in Increasing Rate of DILI

Incidence rates, incidence rate ratios, and adjusted hazard ratios of fulminant hepatic failure in 11,678 HIV-only and 4761 HCV-HIV coinfected veterans

Outcome event	HCV and HIV coinfection		HIV only		HCV-HIV coinfection vs. HIV only	
	Number with FHF	Incidence rate per 1000 person-years	Number with FHF	Incidence rate per 1000 person-years	Incidence rate ratio (95% CI)	Adjusted hazard ratio[a] (95% CI)
FHF, entire cohort	50	2.45	42	1.06	2.30 (1.49–3.55) $P=0.0001$	2.66 (1.74–4.06) $P<0.0001$
FHF, pre-HAART era[b]	8	1.81	19	2.09	0.86 (0.34–2.06) $P=0.75$	0.99 (0.43–2.31) $P=0.98$
FHF, HAART era	18	3.28	7	0.58	5.62 (2.24–15.91) $P<0.0001$	5.86 (2.36–14.50) $P=0.0001$

- HAART and hepatitis C appear to act synergistically in HIV-infected patients to increase the risk of fulminant hepatic failure

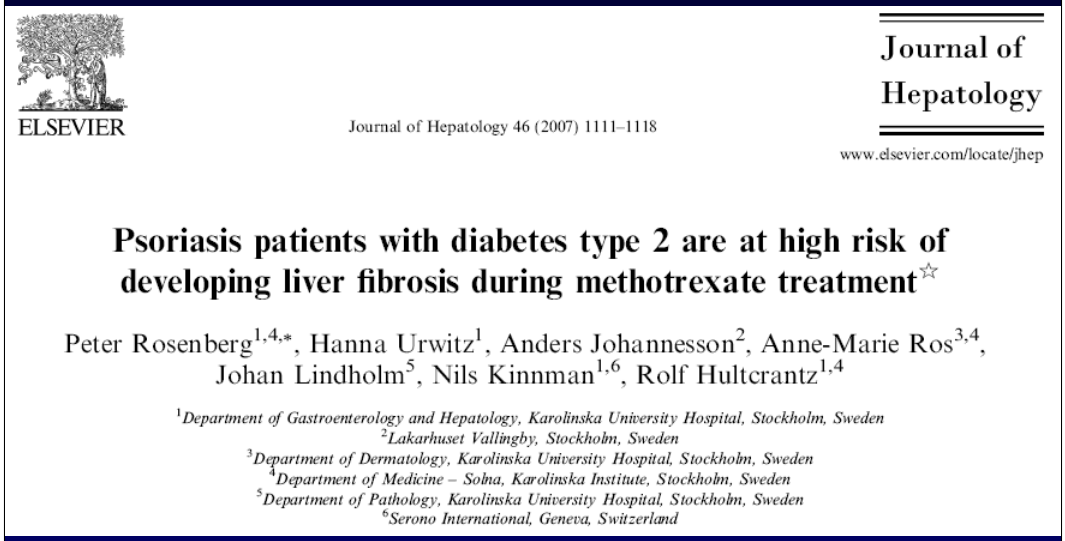
J.R. Kramer et al. Journal of Hepatology 2005;42:309–314

As you can see in this table, in the general group the risk of hepatic failure was 2.6-fold in patients with underlying hepatitis C. In contrast, before the HAART era, there was no increased risk of fulminant hepatic failure in patients with underlying hepatitis C, suggesting that the increased risk of fulminant failure was related to the HAART drugs reather than the underlying viral disease.

And finally when they looked only at patients from the HAART era, there was a 5.86 times increase in fulminant hepatic failure that was clearly drug-induced. They are basically hepatotoxic like many other medications.

The authors concluded that HAART and hepatitis C appear to act synergistically in HIV-infected patients to increase the risk of fulminant hepatic failure.

Role of Underlying Liver Disease in Increasing Rate of DILI



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Journal of Hepatology 46 (2007) 1111–1118

Journal of Hepatology

www.elsevier.com/locate/jhep

Psoriasis patients with diabetes type 2 are at high risk of developing liver fibrosis during methotrexate treatment☆

Peter Rosenberg[1,4,*], Hanna Urwitz[1], Anders Johannesson[2], Anne-Marie Ros[3,4], Johan Lindholm[5], Nils Kinnman[1,6], Rolf Hultcrantz[1,4]

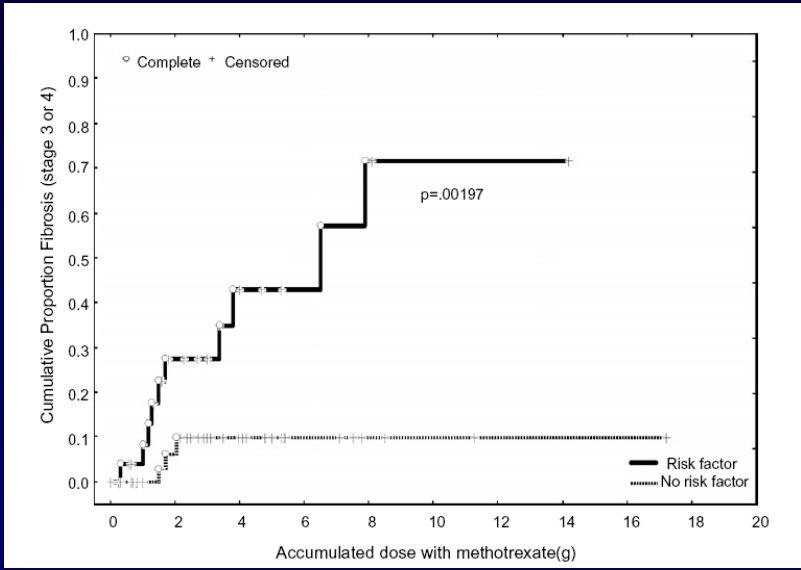
[1]*Department of Gastroenterology and Hepatology, Karolinska University Hospital, Stockholm, Sweden*
[2]*Lakarhuset Vallingby, Stockholm, Sweden*
[3]*Department of Dermatology, Karolinska University Hospital, Stockholm, Sweden*
[4]*Department of Medicine – Solna, Karolinska Institute, Stockholm, Sweden*
[5]*Department of Pathology, Karolinska University Hospital, Stockholm, Sweden*
[6]*Serono International, Geneva, Switzerland*

- 169 liver biopsies from 71 patients on methotrexate

And this is not limnited to hepatitis B and hepatitis C. The following is an example showing how another underlying liver disease, non-alcoholic fatty liver disease, can increase the risk of DILI.

This is a recent publication in the Journal of Hepatology by a group from Sweden. They looked at patients receiving methotrexate for psoriasis. They tried to establish whether risk factors for fatty liver disease such as in diabetes type 2 were associated with increased risk of developing methotrexate-induced liver fibrosis.

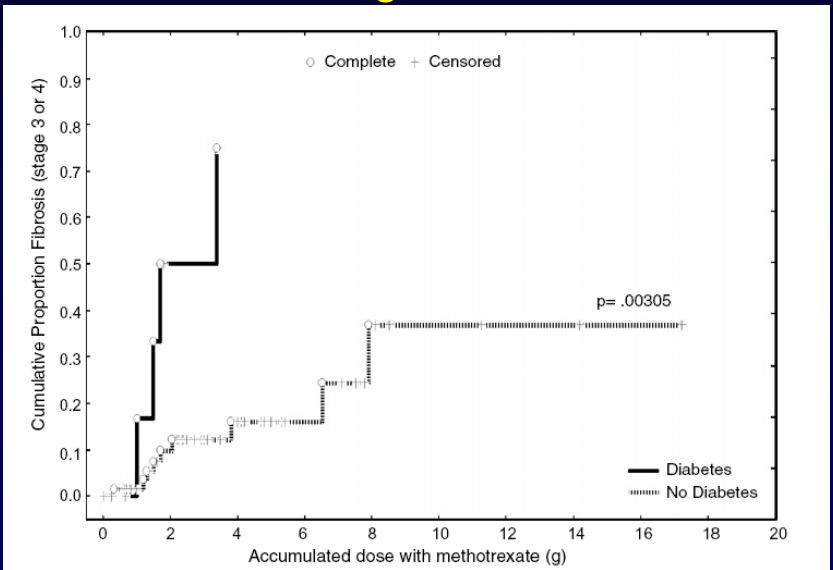
Role of Underlying Liver Disease in Increasing Rate of DILI



Advanced fibrosis (stage≥3) in patients with or without at least one of the risk factors: overweight, high alcohol consumption, diabetes mellitus or viral hepatitis.

The results of this interesting study are presented in this slide. As you can see, patients who had underlying liver diseases or risk factors for liver disease such as high alcohol consumption, diabetes, overweight, or viral hepatitis, had increased risk of developing stage 3 fibrosis due to methotrexate. The difference was about 75 percent, compared to 10 percent.

Role of Underlying Liver Disease in Increasing Rate of DILI



Advanced fibrosis (stage≥3) in patients with or without diabetes mellitus type II.

But when these investigators looked at diabetes mellitus type II alone, which is a very strong risk factor for fatty liver disease, the results were not less impressive. Again methotrexate had a much higher risk of causing stage 3 liver fibrosis if the treated patient had fatty liver disease to begin with, or diabetes mellitus type II to begin with.

Role of Underlying Liver Disease in Increasing Rate of DILI

Conclusion: Patients with methotrexate treated psoriasis and risk factors for liver disease, especially diabetes type 2 or overweight, are at higher risk of developing severe liver fibrosis compared to those without such risk factors

Rosenberg P. et al. Journal of Hepatology 2007;46:1111–1118

The authors concluded that patients with methotrexate-treated psoriasis and risk factors for liver disease, especially diabetes type II or overweight, are at higher risk of developing severe fibrosis of the liver, compared to those without such risk factors. So it looks like underlying fatty liver disease may also be a risk factor for more frequent of more severe DILI.

Increased Risk of DILI in Patients with Underlying Liver Diseases

- Isoniazid/ Rifampin + chronic hepatitis B
- Isoniazid/ Rifampin + chronic hepatitis C
- HIV drugs + chronic hepatitis B
- HIV drugs + chronic hepatitis C
- Methotrexate + alcoholic liver disease
- Methotrexate + NAFLD

This list shopws a few examples of situations where combinations of underlying chronic liver diseases and a superimposed medication lead toa higher risk of hepatotoxicity.

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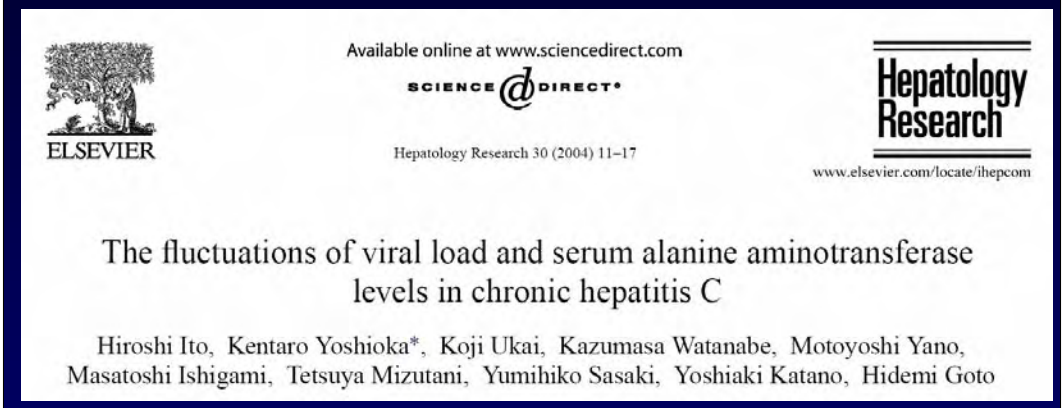
And I'm going straight to point number 4. And here I'm going to switch to completely different problem that we may encounter if we enrollpatientswith underlying liver diseases in clinical studies. It is called spontaneous ALT fluctuations, which is a real issue with some liver diseases. Unfortunately, if that happens during a clinical trial, it may lead to discontinuation of a drug, or even to termination of a study, although it may be completely unrelated to the drug and the real cause is the underlying liver disease. I'll give you just a very few examples.

ALT Fluctuations in HCV Patients



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Available online at www.sciencedirect.com
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Hepatology Research 30 (2004) 11–17
Hepatology Research
www.elsevier.com/locate/ihepcom

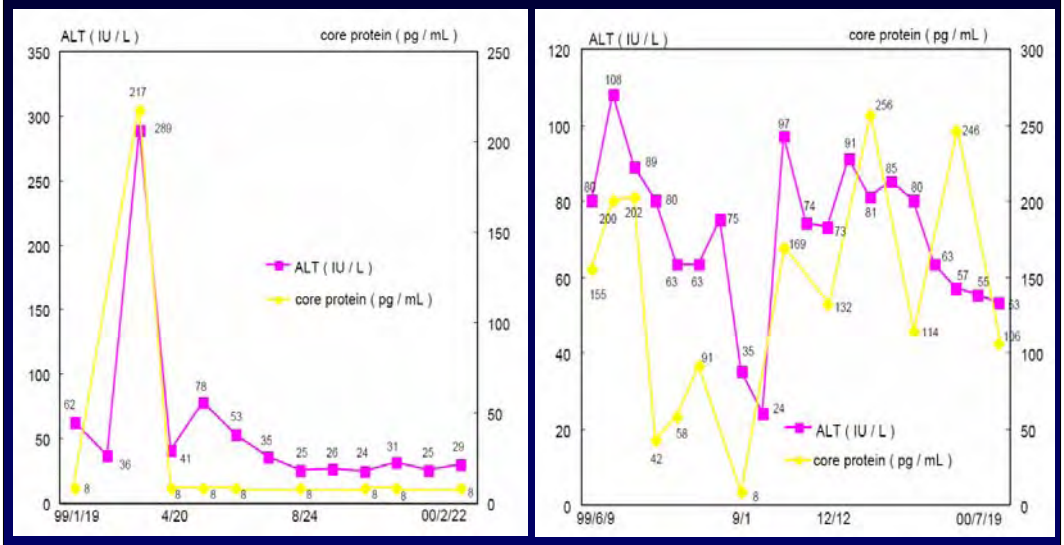
The fluctuations of viral load and serum alanine aminotransferase levels in chronic hepatitis C

Hiroshi Ito, Kentaro Yoshioka*, Koji Ukai, Kazumasa Watanabe, Motoyoshi Yano, Masatoshi Ishigami, Tetsuya Mizutani, Yumihiko Sasaki, Yoshiaki Katano, Hidemi Goto

Hepatitis C is well known to be associated with fluctuations in ALT. These fluctuations are typically spontaneous and have no. clear initiating factor.

Take a look at a this study published in Hepatology, in which a group from Japan looked at ALT levels in patients with hepatitis C who were not receiving any medical treatment.

ALT Fluctuations in HCV Patients



H. Ito et al. Hepatology Research 2004;30:11–17

You can see that ALT may jump from 40 to almost 300, in this case from 30 to almost 120. This sometimes goes with parallel increases in HCV RNA levels, or sometimes without such changes. This could happen in a clinical trial, and may lead to confusion and erroneous decisions.

ALT Fluctuations in HCV Patients

J Gastroenterol 2007; 42:673–680
DOI 10.1007/s00535-007-2078-0

Journal of Gastroenterology

Alanine aminotransferase flare-up in hepatitis C virus carriers with persistently normal alanine aminotransferase levels in a hyperendemic area of Japan

Hirofumi Uto[1], Joji Kurogi[2], Yuka Takahama[3], Kazunori Kusumoto[2], Katsuhiro Hayashi[2], Akio Ido[4], Michinori Kohara[5], Sherri O Stuver[6,7], Akihiro Moriuchi[1], Susumu Hasegawa[1], Makoto Oketani[1], and Hirohito Tsubouchi[1,4]

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[4]Department of Experimental Therapeutics, Translational Research Center, Kyoto University Hospital, Kyoto, Japan
[5]Department of Microbiology and Cell Biology, Tokyo Metropolitan Institute of Medical Science, Tokyo, Japan
[6]Department of Epidemiology, Boston University School of Public Health, Boston, MA, USA
[7]Department of Epidemiology, Harvard School of Public Health, Boston, MA, USA

To se how common this penomenon is, let's look at another Japanese study. The authors of the study looked at the risk of

De veloping ALT fluctuation in chronic HCV patients who had been enrolled with normal levels of hepatic enzymes and with normal liver tests, but only a hepatitis C background.

ALT Fluctuations in HCV Patients

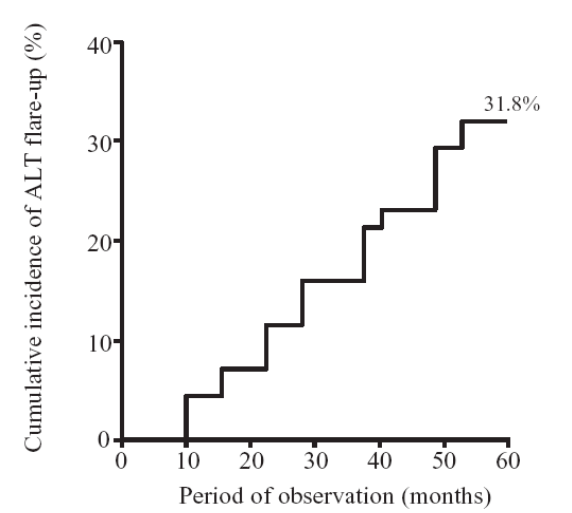

Fig. 1. Cumulative incidence of alanine aminotransferase (*ALT*) flare-up in subjects with persistently normal ALT levels, based on the Kaplan-Meier method

Hirofumi Uto et al. J Gastroenterol 2007; 42:673–680

During a five-year follow-up, they had a risk of 31.8% of having ALT fluctuations. Occasionally, but much less often, there were fluctuations in bilirubin levels. When that happens, and the patient is in a clinical trial, and is getting an investigational drug, what are we doing with this patient? We'll talk about it soon.

Fluctuations in Liver Enzymes

- Chronic hepatitis B
- Chronic hepatitis C
- Autoimmune hepatitis
- Alcoholic hepatitis
- Nonalcoholic steatohepatitis

Enzyme fluctuations can happen in hepatitis C, or in B to a lesser extent, but also can happen in different kinds of liver diseases. For example, autoimmune hepatitis, especially in phases when it is not treated, could also have fluctuations. Alcoholic hepatitis commonly exhibits fluctuations in AST and ALT levels, and even nonalcoholic steatohepatitismay show fluctuations in liver enzymes, although in lower magnitude.

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Another problem we may encounter during clinical trials is flare-ups of the underlying ;iver disease. Some drugs, when combined with certajn liver diseases, may cause activation and flare-up of these diseases, which may sometimes be quite severe.

One example classically is hepatitis B, but there are others. For the sake of time, I'm just going to show one recently published study that looked at hepatitis B patients getting chemotherapy for Hodgkin's Disease.

Flare-up of Underlying Liver Disease

HEPATOLOGY, Vol. 47, No. 3, 2008

A Revisit of Prophylactic Lamivudine for Chemotherapy-Associated Hepatitis B Reactivation in Non-Hodgkin's Lymphoma: A Randomized Trial

Chiun Hsu,[1,2] Chao A. Hsiung,[3] Ih-Jen Su,[4] Wei-Shou Hwang,[5] Ming-Chung Wang,[6] Sheng-Fung Lin,[7] Tseng-Hsi Lin,[8] Hui-Hua Hsiao,[7] Ji-Hsiung Young,[8] Ming-Chih Chang,[9] Yu-Min Liao,[10] Chi-Cheng Li,[11] Hung-Bo Wu,[12] Hwei-Fang Tien,[2] Tsu-Yi Chao,[13] Tsang-Wu Liu,[14] Ann-Lii Cheng,[1,2,14] and Pei-Jer Chen[2,15]

This study compares two types of approaches to management in this patient population: prophylactic treatment versus treatment upon detection of a flare-up. To show you how common HBV flare-up is, I will just show the results of the group of patients who did not receive prophylaxis.

Flare-up of Underlying Liver Disease

Table 2. Incidence of HBV Reactivation and Hepatitis

	Prophylactic Group	Therapeutic Group	*P*-Value
During protocol treatment	n = 26	n = 25	
HBV reactivation	3	14	0.001
Hepatitis flare	4	15	0.001
HBV reactivation and hepatitis flare	2	12	0.001
HBV reactivation and ALT10 × ULN	0	9	<0.001
HBV reactivation and bilirubin > 1.5 × ULN	0	5	0.023
After protocol treatment	n = 26	n = 21	
HBV reactivation	5	3	0.716
Hepatitis flare	7	3	0.475
HBV reactivation and hepatitis flare	4	1	0.362
HBV reactivation and ALT>10 x ULN	3	0	0.242
HBV reactivation and bilirubin > 1.5 x ULN	3	0	0.242
Hepatitis-related death	2	0	0.242

Hsu C, et al. Hepatology 2008;47:844-853

As you can see, out of 25 patients that did not receive prophylaxis, 14 had a flare-up of hepatitis B, of whom 9 had an increase of ALT to 10 times the upper limit of normal, and 5 had an increase in bilirubin to more than 1.5 times the upper limit of normal..

This was clearly related to the effect of cytotoxic chemotherapy on hepatitis V infection.

Flare-up or Exacerbation of Chronic Stable Liver Disease

- Chronic hepatitis B + Cytotoxic chemotherapy
- Chronic hepatitis C + Cytotoxic chemotherapy
- Chronic hepatitis B/C + Corticosteroids
- Chronic hepatitis B/C + Immune suppressants
- Autoimmune hepatitis + Interferon, statins, etc.

Cytotoxic chemotherapy can have a similar effect with hepatitis C, although to a lesser extent. Similar flare-ups of viral hepatitis can be seen with corticosteroids and other immunosuppressive drugs including anti-rejection medications and anti-rheumatoid arthritis agents. In a completely different mechanism, autoimmune hepatitis can exhibit flare-ups with certain medications as well\. A classical example is interferon-alpha, but we see it with statins and other drugs that could potentially lead to an triggering of an autoimmune hepatitis.

Potential Problems

- DILI may worsen a coexisting acute liver disease
- DILI may lead to decompansation in patients with liver dysfunction
- ULD may increase incidence/severity of severe DILI
- ALT fluctuations due to underlying liver disease
  - May lead to early discontinuation of a study drug
  - May lead to early termination of the study
- Flare up of underlying liver disease due to the drug
- Flare up of alcoholic liver disease due to recurrent drinking
- Increase in fatty infiltration in NAFLD patients

When we talk about enrolling patients who are chronic alcoholics, with alcoholic liver disease, we can expectadditional specific problems. As we know, a very high percentage of these patients will relapse and will go back to drinking alcohol even during clinical trials. Unfortunatel, we cannot always be sure if they're doing that or not because the history is not always accurate.

Relapse in Alcohol Dependent Patients

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LIVER, INTESTINE

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Liver transplantation for alcoholic cirrhosis

Table 2 Recurrence of alcoholic disease

Time	Incidence of recurrence	Severe recurrence
< 1/2 year	66.4 %	84.7 % [a]
1/2–1 year	14.3 %	60.0 %
1–2 years	13.9 %	40.0 %
> 2 years	5.6 %	100 % [b]

[a] Four patients with severe alcohol recurrence died
[b] One patient with severe alcohol recurrence died

This slide shows as an example a group of patients followed after liver transplant for alcoholic liver disease. And you can see that in the first 6 months, 66 percent relapsed. This is a common problem, and when a patient with a history of alcohol abuse is enrolled in a clinical trial, there is significant risk that he will go back to drinking alcohol during the study.

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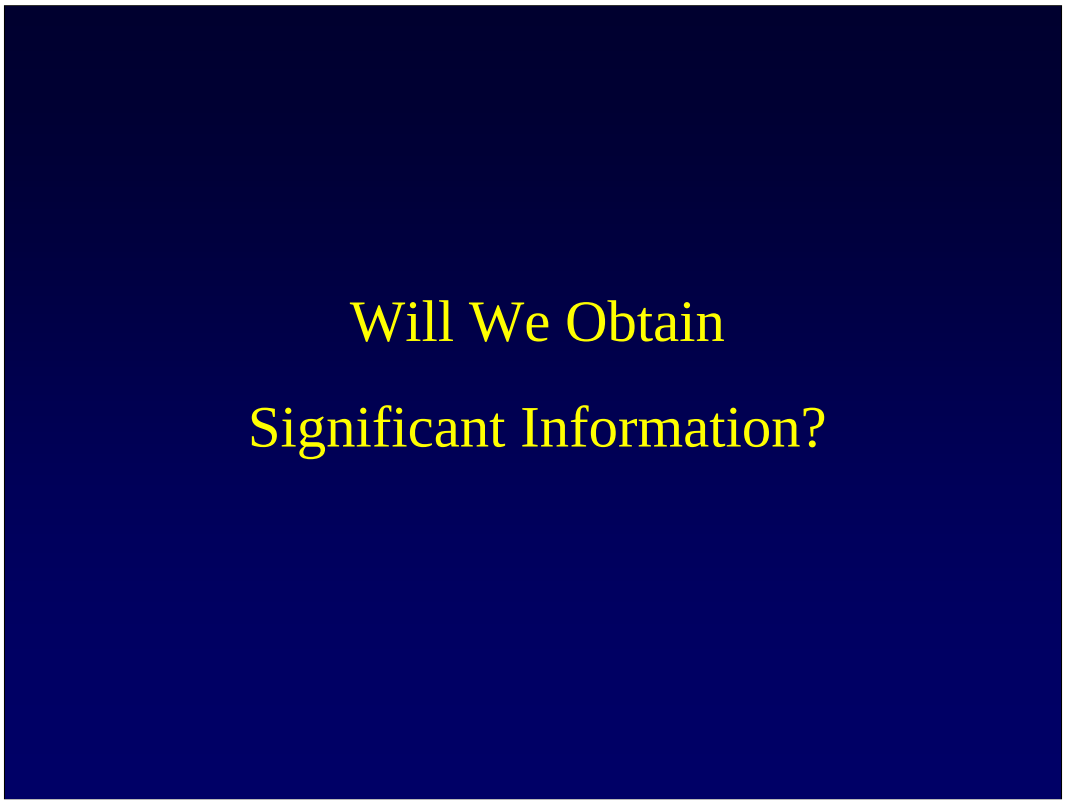
And lastly, how about patients with nonalcoholic fatty liver disease? Well, this may look like a pretty safe group of patients to treat.

Drugs Increasing fatty infiltration

- Methotrexate
- Amiodarone
- Steroids
- Leuprorelin
- Tamoxifen
- Chemotherapy (fluorouracil + irinotecan)

Well, unfortunately, there's a long list of medications, and this is just a few of them, that can actually induce hepatic steatosis, and can actually increase the amount of fat in the liver. The question is, what is the outcome of this medication given to a patient that has already a significant hepatic steatosis maybe with some fibrosis? Does it move the process much more rapidly forward? If the patient presents with cirrhosis or a liver tumor, was it caused by the drug or was it the result of the natural history of his fatty liver?



Let me look at this fro another direction for a second. Let's assume we decide to go ahead and enroll patients with underlying disease in clinical trials. How much information are we going to obtain when we actually enroll these patients?

Chronic Liver Disease
Prevalence in United States

Disease	Out of 500	Prevalence Rate
Chronic hepatitis C[1]	9	**1.8%**
Alcoholic liver disease[2]	< 4	**0.7%**
Hemochromatosis[3]	< 3	**0.5%**
Chronic Hepatitis B[4]	2	**0.4%**

1. Alter MF et al. *N Engl J Med.* 1999;341:556 562.
2. Venkataramani A, Sorrell MD. In: Maddrey WC, Feldman M, eds. *Atlas of the Liver.* Philadelphia: Current Medicine;1999:9.0.
3. Adapted from http://www.nhlbi.nih.gov/new/press/01/09 -25.htm. Accessed 11/01/02
4. McQuillan GM et al. *Am J Public Health* 1999;89:14-18.

Well, let's first look at the numbers. How many patients with hepatitis C do we have in the United States? Well, for formal percentage is 1.8%. That means that if we have a clinical trial of 500 randomly selected patients, we'll probably have 9 patients among them. But wait a minute. Out of those 1.8 percent, less than half are actually diagnosed, and in some areas 80% are not.. So we're going to have less than 4, and out of these 4, the primary care physician may tell 2 not to enroll because you have liver disease. So we probably have 2. Now how do we randomize those two? Think about this.

Take a look at the alcoholic liver disease diagnosed in the United States in about 0.7 percent. That means that out of 500, we have less than 4. Two of them will not tell you that they alcoholic liver disease by the way. How do you randomize them?

And how about chronic hepatitis B? In the U.S. about 2 patients out of 500. Well, if there're 1,000 patients in the study, we would have maybe 4. I calculated that back at the hotel. (Laughter.) So how do you randomize them?

How about hemochromatosis or Wilson disease, where we may not have even 1 in a large clincial study

A Hy's Rule Levels in a Study Patient with Chronic Hepatitis C

1. DILI?

   Discontinue study drug. Discuss discontinuing the study

2. Interaction drug + hepatitis C?

   Discontinue study drug. Discuss Excluding HCV patients

3. Exacerbation of hepatitis C?

   Start PEG-Interferon + Ribavirin

4. Unrelated to either study drug or HCV?

   Work up and treat for hepatitis A,B, AIH, ALD, etc.

let's say we did enroll patients with hepatitis C and we do have this precious patient that we follow very closely and all of a sudden, he has Hy's Rule level, not Hy's Rule abnormality yet, just Hy's Rule level. So it should be called Hy's Rule only if it will be proven to be the drug, but I'm going to just submit to you that he has ALT of three times the upper limit of normal and bilirubin of two times the upper limit of normal. Is it DILI? Well, if we think it's DILI, then we need to discontinue the study drug or maybe discuss discontinuing the study .but how can we tell the difference? I cannot tell the difference. I've been a hepatologist for years and I cannot tell the difference; it's very complicated.

And let's say we decided it's an interaction. What do we do then? Again, do we discontinue the study drug? Do we exclude HCV patients in the future from getting this drug? And how about if we think it's exacerbation of hepatitis C? Then do we start giving interferon? Do we exclude the patient from the study? And how about if we think it's not related to other study of HVC? Then we have to work up these patients very carefully because hepatitis C goes with alcohol, with hepatitis B, and with other diseases.

So what are we going to do exactly? This is something we need to be very clear on before we enroll this patient.

Long Term Conclusions

1. DILI?

   Ban HCV patients from receiving the drug?

2. Interaction drug + hepatitis C?

   Start a clinical trial treating 1,000 HCV patients?

3. Exacerbation of hepatitis C?

   Ban HVC patients from receiving the drug, and start a clinical trial treating 1,000 HCV patient?

How about long term conclusions? Let's say we decided this HCV patient had drug-induced liver disease. Does that mean in the long run, we ban HCV patients from receiving the drug? What does it mean exactly? Or let's say we think it's interaction between the drug and Hepatitis C. Does it mean we'll start a clinical trial for Hepatitis C patients? Should we enroll 1,000 HCV patients to look at this drug.

And how about if it's just an exacerbation of hepatitis C? Then do we both ban the drug and start a clinical trial. You need think very carefully about what we are going to do with this data once it becomes available.

Risk Benefit Ratio

Risks

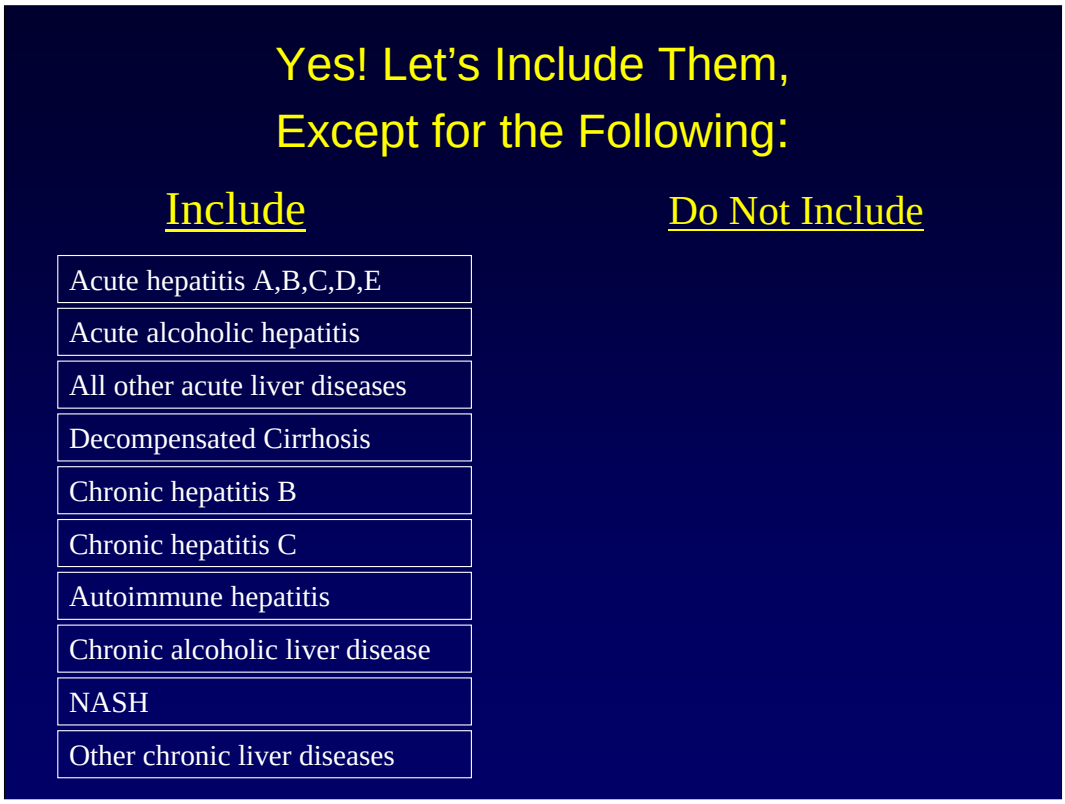
- Increased risk of severe DILI during clinical trials
- Misinterpretation of results
- Erroneous discontinuation of study drug
- Erroneous discontinuation of study
- Abandoning a good drug for the wrong reasons

Benefits

- These patients are likely to receive the drug post marketing
- Reveal potential problems during clinical trials rather than post marketing (?)

So again, enrolling patients with underlying liver disease makes sense because they are likely to receive the drug post-marketing, and we want to reveal problems before the drug is approved.

But look at the risks. Is it worth it? We may be increasing the risk of severe DILI. We are increasing the risk of misinterpretation of the results, erroneous discontinuation of a study drug, erroneous discontinuation of a study, and abandoning of a good drug for the wrong reasons. These are all risks that we need to think about.



So just looking at it from a different perspective, in general again, it looks like a nice idea. But let's think about the specific groups of patients. Acute Hepatitis A, B, C, D, E we decided not good. Acute alcoholic hepatitis, not a good group to enroll. I think we all agree on that. Oother acute liver diseases? Not a good idea.

Decompensated cirrhosis, well, probably we will all agree that this is not a good group to enroll. Chronic hepatitis C again, fluctuations, maybe flare ups, many of them are undiagnosed and by the way, when hepatitis C patients is just known as hepatitis C, the levels of ALT, they do not tell you what the severity of the liver injuries. It could be anywhere from mild inflammation to advanced cirrhosis and you will not know. It is just in your study.

How about autoimmune hepatitis? It could be a problem. How about chronic alcoholic liver disease? Well, many issues with those patients and always the potential risk of having one that you don't know, in effect, full blown drinking.

How about NASH? Some are good in the beginning but also some problems with drugs that cause fatty liver disease and some problems with the fact that these patients may actually have drugs that are moving forward in their effects like methotrexate, when you have fatty liver disease.

Well, how about other chronic liver diseases? Well, patients with Wilson disease, hemochromatosis, alpha-1 antitrypsin deficiency. Who wants these rare very esoteric diseases in the study? God knows how they will respond. (Laughter.) Well, maybe there are others, maybe but we're not sure yet.

Summary

- Including patients with pre-existing liver diseases in clinical trials carries multiple potential risks and logistical difficulties
- These difficulties would make the practicality and feasibility of this approach highly questionable in many cases
- Inclusion of patients with pre-existing liver disease in clinical trials-
  - should be carefully discussed on a case-by-case basis
  - should not be adopted as a swiping recommendation

To summarize, I'm going to be very accurate here because I know this is recorded.

Including patients with preexisting liver diseases in clinical trials carries multiple potential risks and logistical difficulties. These difficulties would make practicality and feasibility of this approach highly questionable in many cases.

So inclusion of patients with preexisting liver disease in clinical trials should be carefully discussed on a case-by-case basis, preferably with a hepatologist, and should not be adopted as a sweeping recommendation.

Summary

Zymurgy's First Law of Evolving Systems Dynamics:

Once yo pen a can of worms, only way to recan them is se a bigger can.

And lastly, I want you to remember, if we do involve patients with liver disease, we are actually opening a can of worms, and I want you to remember this. Zymurgy's first law of evolving systems dynamics says:"Once you open a can of works, the only way to recan them is to use a bigger can." (Laughter.)

Thank you very much.