P:LEE (discussion)

DR. PEARS: Thanks, Will. Does anybody have another perspective or some particular questions about those cases that he just brought up or some comments on them? The microphones should all be working. If not, we've all been trained in the same sign language you have. So we'll be able to recognize it.

DR. AVIGAN: Some of these cases are highly confounded. In the case of duloxetine-induced liver injury, alcohol was a question mark. When you look diagnostically at biochemical profiles, alcoholic hepatitis has a slightly different profile of elevations of serum ALT and AST than do most drugs. Would the sky-high transaminases sway you with regards to the contributory role of the drug versus the alcohol, and how would you use that in formulating a hypothesis about the relevant contributions to liver injury of both agents? That's one question. The second question is, as you incorporate subsets of patients who might have other risk factors to look at what you get in a clinical trial, you pointed out that statistically you might have small numbers in each subset. At best the DILI signal may be suggested but not verified. It's not necessarily going to be proven at that point. So you'll have signals without definitive conclusions. The question is what's your game plan? Do you then propose that these questions will be settled in the post-market setting in a large safety study,

and how would you configure that? What would be the pharmacovigilance plan to definitively address the question? Part of the problem here is you're in a catch-22 of looking for signals but they're not getting definitive answers because specific strata are underpowered.

RECORDER: Sir, can you identify yourself?

DR. AVIGAN: I'm Mark Avigan.

RECORDER:: Thank you.

DR. LEE: Mark, yes. This is a tough one. I think the point to be made about the aminotransferase levels were that the vast majority of these were typical alcoholic hepatitis numbers, like AST of 200, ALT of 50. So that was easy to say, okay, that's that. There might have been one or two where there was an AST of 500 but then they've been taking some acetaminophen. You know, there were all kinds of confounders in there.

I don't know what to do about the other issue, about the subgroup and what you do but, but I think it was clear to us as hepatologists that in the majority of these cases, that the drug appeared to play no role, meaning that it was a binge, it had started at an interval ahead of the admission to hospital and that it all fit very nicely once you put it in that perspective.

I think the post-marketing situation is where we need to be creative. John, that's the topic for the meeting next year, that's going to be about post-marketing vigilance and figuring out what we can do better. But I

think you now task the companies. They have as the carrot the provisional approval. You task companies to figure out whether there should be weekly testing, you know, I mean it would be onerous, of course, but if the drug is that good, it has that carrot.

DR. PEARS: Sir, identify yourself.

DR. THEODORE: Dickens Theodore, GlaxoSmithKline. Well, you made a point about engaging the agencies to think about expanding their criteria for some of the populations. And I guess with different agencies, their views can be different. I certainly have been in the situation where some agencies say our primary concern is for the patients in the population that you're studying right now. In a clinical trial, you have responsibility to protect the subjects, and while you may want to expand the population, some agencies think that's better served with studies after marketing authorization. How do you deal with that?

DR. LEE: Well, that is surveillance and that's the argument for doing it preapproval in a way lets them all in. Let's see what happens, because post-approval, nobody's minding the store, nobody's looking. I think that's the argument, the full side of the argument. The other thing is the anti-infective committee had to deal with Ketek, but all of the Ketek issues were not infectious disease issues, or most of them were not infectious disease issues.

So again I think my advice to the FDA when they

use outside consulting, that they use people like me and Paul Watkins and so forth, but they almost need to use more rather than having the panel, the 12 ID people and me over in the corner with no vote.

DR. PEARS: Thanks. We'll take one more question from Naga Chalasani and then we'll go back to the presentations.

DR. CHALASANI: Thank you. Naga Chalasani from Indiana University. Will, let me clarify this. Your statement about no cases of duloxetine in your review cases?

DR. LEE: Right.

DR. CHALASANI: My question to you in the ALF, the study group, were there any cases of duloxetine related liver failure?

DR. LEE: I don't think we had a single one. I think you have one or two in DILIN.

DR. CHALASANI: We have five cases of duloxetine-related liver injury recruited into the DILI Network. At least two are from our IU site. Both are relatively clean and they've both been adjudicated to become relatively high on the causality. I don't know about the other three cases.

DR. LEE: Sure.

DR. CHALASANI: This is, you know, later on in the post-marketing period.

DR. LEE: Sure.

DR. CHALASANI: The questions about the liver diseases, whether you want them or not, they are there in some clinical trials. For example, if you're studying a diabetic compound, nearly 80 percent of the population are type II diabetics with fatty liver. If it is just based on an ALT, I think to a large degree we are fooling ourselves.

So my point is that fatty liver is a different thing compared to viral liver disease where there is risk of flare up during the clinical trial. Do have any comments or thoughts?

DR. LEE: Yes, I think your arguing for more inclusiveness is what I'm hearing, I think.

DR. CHALASANI: Yes. I mean fatty liver patients are there, whether you want or not. So include them.

DR. LEE: Now I would say include viral hepatitis, too, provided you know what you're dealing with. I mean we don't see violent flares of hepatitis C. We do see violent flares of hepatitis B but again, there's a treatment for that, and it's well recognized and it's only in the setting of immunosuppression essentially. So I think you can deal with hepatitis C and B --

DR. CHALASANI: Thanks.

DR. LEE: -- as well as evaluate it.

DR. PEARS: Okay. Thanks for the questions and thank you, Dr. Lee, for answering them.