**Session IV: The Real World: Post-marketing DILI**

Moderators: Christine Hunt and John Senior

- Finding cases in the post-marketing environment  
  Christine Hunt
- Analyses of large databases: Kaiser Permanente  
  Craig Cheetham
- Epidemiologic approaches: OMOP  
  Judy Racoosin
- Modulation by concomitant medications  
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- Should we propose a standard of care for DILI cases?  
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General discussion IV

Adjournment
Session IV: The Real World: Post-marketing DILI.

LANA PAULS: We have one more session today, Session 4. And that is the Real World: Post-marketing DILI. And our moderators are Chris Hunt and John Senior. Before we get to them, of course I always have announcements. The slides that you have seen will be posted in about four to five weeks. That's one of the reasons that we gave you the little pin drive so you could have them earlier. In addition, I have received several requests for people to have the list of registrants. My intention was to send that out to all of the registrants. If for some reason you do not want your contact information sent out to the masses, please email me no later than close of business on Monday, and I will make sure to delete your name from the list or a number or something. So please make sure that you do that. And last but not least, for those of you who have come to a number of these meetings, I appreciate it. We are already in our planning stages for meeting 2012. John already has all these wonderful ideas in his head. And it will be about this time next year. And it will be here. I want to make a plea, for those people who did not stay here at the NLC in the sleeping rooms. One of the reasons that our costs are so low every year for this meeting -- $250 and $500 -- is because we defray a lot of the costs by the people that stay here. So if you plan on coming back next year, I'm making a plea that you do try and stay here as well. So thank you.

DR. SENIOR: Please understand that we have no grants to fund this. The FDA gives us no money. PhRMA gives us no money. AASLD takes our money and uses it for other conferences. So we have to pay our own way. Lana does a wonderful job of making deals with the Labor College here. But the Labor College has also raised its rates. So understand where we're coming from. We pay no honoraria to anybody. We pay travel money only to invited academic speakers, not the government, not the industry. So we keep our costs as low as we can. We very rarely import academic speakers from Europe because we can't afford it. Not that we're not interested in what they say, it's just a reality. So understand that we're doing the best we can. And we absolutely are astonished at the wonderful turnout. Look at this. We had 100 people last night for an extra session, 200 people during the day. Amazing. So it's really a very good thing. As for the idea of sending out email addresses, we're not going to send everything out and your phone number and all, but just your email so you can get in touch with each other and clarify points and interact productively and constructively. So with that, Chris --
Christine Hunt  Finding cases in the post-marketing environment

DR. SENIOR: And thank you, Chris. I think we'll have the four other presentations and then have a final half-hour of discussion. We'll bring one chair up on each side so we'll have places for the whole panel to speak, discuss, and answer questions. Let's go with Craig now.

DR. HUNT: I want to present Dr. Craig Cheetham from Kaiser Permanente Southern California, who will be sharing some very exciting new results from the Kaiser analyses.

Craig Cheetham  Analyses of large databases: Kaiser Permanente

DR. HUNT: Thank you for an excellent talk. We'd like to introduce our next speaker -- Dr. Judy Racoosin, who's the scientific lead for the Sentinel Event Initiative here, to present the Observational Medical Outcomes Partnership Data. They're looking at a broad range of scientific methodology, so nicely complementing the talk about which we just heard that looked at both electronic medical records and claims databases. Welcome.

Judy Racoosin  Epidemiologic approaches: OMOP

DR. SENIOR: Thank you, Judy.

DR. HUNT: We'd now like to introduce Dr. Ayako Suzuki who shared some data last year. She's going to be building on that and actually showing data from multiple drugs -- hypothesis-generating data -- and then further examining this data using electronic medical records. So exciting new developments.

DR. SENIOR: While Ayako is approaching, I think all of us who present slides realize the almost irresistible urge to tinker with our slides at the last minute. So Judy, you are understandably forgiven for trying to submit a green set.

Ayako Suzuki  Modulation by concomitant medications

DR. HUNT: Thank you, Ayako. Our last speaker is Dr. Leonard Seeff who is kindly going
to share with us the standard of care of DILI -- some initial ideas. Thank you.

**Leonard Seeff**  Should we propose a standard of care for DILI cases?

**Discussion IV**

**DR. SENIOR:** Thank you, Leonard. Please stay and we'll invite the other speakers up to the podium. And if someone will bring one more chair on each side, we'd have a place for each one.

**DR. BOURDI:** Could I start with a short question here?

**LANA PAULS:** Sure.

**DR. BOURDI:** Just a suggestion, instead of going all these steps, don't you think it's much easier to get the blood from the patient before taking a drug and save it and then afterward you then compare it to what's happened later? Because it's not expensive to have a sample of the blood from the patient at the hospital and save them and then you can compare transaminase or whatever you have weeks later when you have disease.

**DR. SEEFF:** I guess it depends on how severe the disease is. What I neglected to say is that if you are concerned, I think you need to get a diagnosis as quickly as possible. You have two options. One option is to say I'll choose an upper limit of normal of say five or ten times the upper limit of normal and stop the drug, evaluate to see whatever causes there are, and if you can find another cause, you may want to give the drug back. But I think that if you're concerned about the fact that this may be a serious case, you've got to get a diagnosis as quickly as possible. I understand that it may take time in order to get this information. But you can usually get that back within a couple of days, I think, to make the diagnosis. So what you are suggesting is that you can stop the drug or --

**DR. BOURDI:** I'm suggesting that a patient before even getting the drug before the treatment have a blood sample.

**DR. SEEFF:** Oh, oh.

**DR. BOURDI:** And then if something happened, you can compare the blood to what's happened in the control.

**DR. SEEFF:** I mean, it would be wonderful if one had baseline -- you're talking about
baseline values before starting the drug to see whether -- of course. I don't know whether that is a routine view in everyone's mind that every person who starts on a drug should have a baseline value. I think it would be wonderful if that were the case. Certainly if it's a drug that is known to potentially cause hepatotoxicity, I do think you need a baseline value. That doesn't mean to say by the way that if it's abnormal that you can't use it because the question is are people who have underlying liver disease more likely to end up with a DILI than those not. And I'm not sure what the consensus view is. But I think many people feel that there isn't a greater likelihood. It can be a problem because it's -- making the diagnosis then becomes very problematic. But I agree with you that one could have baseline normal values to start off with. That would be wonderful.

DR. SENIOR: I have a question for Chris. Chris, you mentioned that hospitalists are not always making a diagnosis of DILI or they're making it wrongly when it's just assuming it's the drug. Now I was a hospitalist for 17 years at Philadelphia General Hospital and Graduate Hospital, and I cared for about 10,000 or more patients. But I was never called a hospitalist. Who are these people? Is there any way to reach them? Do they have a journal? Who are they?

DR. HUNT: I mean, it's an official specialty now. People are just hospital-based.

DR. SENIOR: How can we teach them to make a diagnosis? Can we publish an article in their journal?

DR. HUNT: I honestly thought somebody in this forum probably needs to consider further education of general practitioners. I actually sent a note to the American Family Physicians to say I'd be glad to write a quick review on DILI just so family practitioners understand what DILI is because I really think there's a general lack of awareness. It's not the top issue that people need to be aware of. But it's the kind of thing that people need to think about when these events happen and what are the potential sequelae. But in any event, what are people's thoughts about DILI education in general?

DR. CAI: Sorry. My question's not on this. But I want to have an opportunity to ask the panel. So far off the presentation using real-world evidence whether it's spontaneous reported adverse event or electronic medical records. This is really fascinating because we often face challenges and those databases are low quality. EMR is now mature. What about our meeting data, confounding factors? I think those studies show some promising preliminary results that you can generate valid hypothesis of risk. So maybe after this comment, thank you for the presentations. And maybe a question is how did you address those challenges, particularly the
confounding factor? I think the data issue we can leave aside.

DR. CHEETHAM: Well, we actually handled the confounding factors by eliminating all of them in this first look. We have that data. And we have that other 400,000 patients that we can look at and evaluate. But clearly the first step was to take a look and see what do we have and can we use the data. And so as we move forward, now we've got to try and see in a more rigorous -- and apply a RUCAM rule or applying some other kind of algorithm, can we actually better identify these people than chart review those patients and actually see how we're doing with the algorithm.

DR. CAI: Before I hear from other panelists, they're still many unknowns such as the dietary herbal supplement or other lifestyle factors. And even co-medication or co-morbidity base may not be complete from the medical claims databases.

DR. CHEETHAM: No, I think that's clearly an issue also. And I think I mentioned it briefly. But at least in our electronic medical record, there's a way to capture over-the-counter medications and herbal products and things like that. But my sense is that when a patient comes into the clinic and is asked or when a physician asks a patient or a provider asks a patient what medications are you taking, those things don't necessarily get recorded very well. So even though we can pull them out, we don't know how valid those things are because nobody's every really done any validation against that. That's clearly a thing that needs to be done.

DR. SEEFF: I must comment on that. I agree with you completely. To ask what medications are you taking leaves out herbals and dietary supplements. You have to specifically ask are you taking herbals, are you taking dietary supplements, because many people just don't think these are medications and sometimes are not even really willing to admit their use unless you really pressure them. And we've had instances of clear cut cases of drug-induced liver injury -- I've seen -- due to herbals in which we've had to ask the patient three or four or five times before they're willing to admit to them and it fits.

DR. SENIOR: And even worse, they don't even necessarily tell you about stuff they buy in the grocery store which is not a prescription. It's just a generic. It's over the counter. And it includes such things as acetaminophen.

DR. RACOOSIN: I was just going to comment that we make a distinction between active surveillance and a full pharmaco/epi-type study. So in many ways, we recognize that there are limitations to these large databases, but we want to try to use them as effectively as possible to
point us in the right direction. And so we know that we won't be able to get OTC drugs and herbal and what not. But to the best of our ability to use the information that's available to point us in the right direction and give us a sense of do we need to do more to look at this particular exposure and outcome, or does there not appear to be that much evidence to support that concern and we can do sort of our standard monitoring. So we're still trying -- I'm speaking a little bit more from the FDA Sentinel perspective here -- but we're trying to figure out where that line is between what is enough, how big an evaluation is an active surveillance evaluation to get us actionable information to make a decision about how to further evaluate a question. So I think your point is well taken that these data sources are designed for payment purposes and for clinical care, and they're not designed necessarily for public health surveillance. And so we have to use the data to the best of our ability recognizing that there are some questions that are going to need more in-depth study.

PARTICIPANT: I'd like to spin the last question a little bit differently. And it's a question for Dr. Cheetham. Kaiser Permanente is clearly one of the most sophisticated health care systems in the country. It's large. It now has an electronic medical record in a number of the Kaisers. But from a public health perspective, the analysis that you've done is pretty much sort of a passive surveillance approach -- the retrospective approach looking at characterizing presumed DILI. Is it feasible for Kaiser to become an active surveillance system? The specific questions I have, in order to be informative about DILI, there's a real timeliness issue. Is it possible in real time to be able to flag cases, to then send a query to provider with some guidance on specifics. If it's a patient who fulfills certain criteria and there're some tests to consider, and simultaneously and ideally to contact the patient, because you really need to get additional information from the patient, including their use of alternative and complementary medicine as well as some nutraceuticals.

DR. CHEETHAM: No. Very good question. And I am in pharmacy operations in Southern California. And the world that I live in, the data are refreshed on a daily basis. So at 3:00 o'clock in the afternoon, I know everything that had been prescribed to that patient, all the clinic visits, all the laboratory results that have been done as of midnight the day before. So clearly, there is that ability to do that. We're taking this at a step-wise progression, right? Can we develop an algorithm that gets us close, right? And if so, the next step would be clearly can we flag these patients, then can we do the outreach to the patients. An excellent question. I think it's clearly
possible to do that.

DR. WONG: Hello, Lisa Wong, Genentech. As an epidemiologist, this was a really informative session. I think I agree with previous commenters about just in terms of the availability of data and the availability of diagnosis, laboratory results. And one question I had for Judy was just in terms of data sets that necessarily have first of all laboratory results or maybe partial laboratory results, is that something that you've looked at and can characterize?

DR. RACOOSIN: The databases that were included on the slides are the ones that had laboratory data available because we wanted to include that definition that required the laboratory abnormalities. So there are ten OMOP databases in all and only three or four of them have laboratory data. So we're more limited in the other ones to the degree that we can get to -- we can see whether a laboratory test was ordered, but not see a result. Is that the question you're asking?

DR. WONG: My question sort of stems -- because we were looking within a cancer population and really trying to characterize possible Hy's law cases using the laboratory test criteria. And when we looked at just sort of claims-based data -- you have a small portion of patients who actually have laboratory tests. But when you look at the number of laboratory tests that they have per patient, I think the median was one per cancer patient population which seemed really unusual because you would expect them to be getting multiple tests. Then we went to an integrated system similar to Kaiser Health that really has all that complete data. And there we would see the median number of tests available around five or ten which makes more sense. I think that's one of the things that would have complete data that makes it valuable. And then I have a second question for Dr. Senior. In terms of the FDA guidance -- and I know yesterday's evening discussion -- focused on how it was really applicable to pre-clinical, clinical pre-marketing development. Do you see any of the aspects of the guidance applying to a post-marketing setting -- spontaneous reports?

DR. SENIOR: We have not even attempted to write a guidance for post-marketing management in the real world. We have focused only on the clinical trials. We're going to keep trying to improve that. And we invite your written comment to the docket. So please send in a thoughtful comment. But we can't get into the post-marketing world until we at least resolve the pre-clinical or the clinical pre-approval control trial.

DR. WATKINS: Question and a comment. Wasn't the purpose of OMOP to see whether
you could in retrospect pick up signals that we now know or believe existed? That would answer the question whether you really need to know about lifestyle and herbals and things like that. For instance, with a drug like Ketek, when you go back retrospectively in these databases and compare your various criteria for liver injury after starting Ketek versus starting another antibiotic, I assume that is what OMOP’s doing, correct?

DR. RACOOSIN: Today I didn’t talk about the main part of the OMOP results. I talked about the development of this tool for characterizing populations with the focus on acute liver injury population. But the main part of the OMOP results -- and I would refer everyone to the OMOP website because you can actually listen to presentations and listen to the audio and look at the presentation of the methods results. Essentially it was to test these ten methods across these 9 true positives and 44 true negatives to see how well these methods were able to pick up what we believe to be true. Actually antibiotics and liver injury was the pair related to acute liver injury. And you can go and see how well the various methods function in the various databases to identify that particular pair. The performance of the methods was rated on a number of different scales. And just in a one line, methods performed highly variably to identify those pairs. Some pairs were identified very well and very consistently across the methods and databases like warfarin and bleeding and ACE inhibitors and angioedema. And there were others that were not as successfully identified. Yes, the goal is to measure the performance of these methods to identify known associations. The reality is that that was highly variable -- how that performance was actually observed.

DR. WATKINS: Do you have a summary of how it works for a known hepatotoxicity?

DR. RACOOSIN: Patrick, do you want to address that? I wouldn’t say that we have summary statement because we have ten methods and ten databases. And each method has anywhere between 24 to 150 different parameter settings. So --

DR. RYAN: What we observed specifically related to our liver injury cases is there were methods in an active surveillance context that could identify a statistically significant association between antibiotics and acute liver injury. It was highly variable to which of the seven definitions were used and the particular epidemiologic design that was applied. Probably more troubling though was applying those same methods to acute liver injury for negative controls -- drugs that we don’t expect to see a relationship. In many instances those same methods that positively found the effect of antibiotics also found an effect that shouldn’t have been there which at least
should give us significant caution that I'm quite optimistic we can use these data sources to identify these effects. But we have to make sure that we're not just identifying all drugs as culprits of drug-induced liver injury, but instead we're really developing tools that can discern between the true effects and what should minimize false positives.

DR. WATKINS: And then just the comment. We have spontaneous adverse events which have incomplete information. Only about ten percent or less are reported. And then you've got these wonderful signal detection things that show a lot of promise but are going to have a challenge with very rare events, I think, like DILI. And it seems to me the logical thing is to have a hybrid of the two which is in the 100 million electronic records, the organizations that have them -- a physician -- to be able to press a button, say I think this is DILI. And then he doesn't have to record all the information. You can actively go into the electronic medical record and extract all the information that you'd want. Because it's simply unrealistic to think a busy practicing physician's going to know everything you're going to want and deal with the hassle of the communications to try to get everything you want. That's just a comment.

DR. SENIOR: We're rapidly running out of time. We may have one last question. But before that, Ayako, how does the VigiBase compare with the AERS system of this country? The VigiBase is strictly European?

DR. SUZUKI: No. I understand that the majority of the cases are from North America. So maybe half of the cases are in AERS. But the reason why I used the WHO VigiBase is the VigiBase had larger number of cases and 3D pair which impact the stuff --

DR. SENIOR: Okay. Last question.

PARTICIPANT: Okay. In last night's session, there was a question asked about -- or there was a comment made that there was a need for a time window on the Hy's law definition. And on your -- this is to you, Judy Racoosin -- about the acute liver injury definitions that you have on I guess the last two that were down toward the bottom of the slide. You had a time frame of less than seven days in there, I believe -- the elevated AST and the ALTs. Where did the seven days come from because it's not in the guidance I don't believe?

DR. RACOOSIN: Patrick, do you recall how that came to be?

DR. RYAN: That's actually the real practical issue when we think about these guidances and how to go about applying them to these observational databases is the guidance don't give us rules about how it's actually going to show up in the data. So the seven days were really based
on our clinical team looking at it and thinking that that's reasonable and then looking in the data to see how often and frequently we could see the ALTs and the bilirubins kind of co-occurring. Originally we actually specified it without a time window, just saying well, if you see a person with an elevated ALT and an elevated bilirubin, we'll call it an event. And what we noticed was a huge number of those people have an ALT and then three years later might have a bilirubin for some unrelated reason. And so what we found was oftentimes when there is a clinical work-up of these folks, the liver function tests more broadly -- ALTs, bilirubin and all seem to be co-occurring at the same time. But don't take the seven days as gospel or rule. It was simply the heuristic we happened to apply to try to investigate this.

PARTICIPANT: Okay. Thank you.

DR. SENIOR: Thank you all for coming and for participating so actively right up to the last minute. It's been a wonderful conference. Thank you all. (Applause.)

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