G:UETRECHT (discussion)

DR. SELIGMAN: We have time for a question or two.

DR. UETRECHT: Okay. I tried to make it short so there would be time.

DR. SELIGMAN: Any questions for Dr. Uetrecht?

DR. SENIOR: Jack, if you have a liver injury that does not show eosinophilia, rash or fever, are you less concerned about a rechallenge? Does the absence of those markers ease your concern?

DR. UETRECHT: You know better than I. Where we have data, and with isoniazid there is a clear benefit, it works in most cases as you said. Pyrazinamide, again as I said, those cases, the ones I've seen have been really nasty reactions. I wouldn't rechallenge those.

DR. SENIOR: Is it the pace of the reaction or the associated phenomenon make the difference?

DR. UETRECHT: The ones that have the longest delay sometimes seem to be the worst and again, that may be a factor or a feature of autoimmunity. That's speculation obviously.

DR. SELIGMAN: We'll go ahead and take one more question.

DR. CHALASANI: Just one more question.

DR. SELIGMAN: Yes.

DR. CHALASANI: Excellent talk, Jack. You said something about wanting to do human studies. Just what exactly do you want? We have many cases of DILI and different kinds of

phenotype and some frozen tissue and serum. What exactly would be ideal in your estimation?

DR. UETRECHT: I'm looking for IL-17. We have less experience with IL-17 because it's fairly new, but usually cytokines, if the sample is frozen quickly and properly, cytokines will be stable. So I just need frozen samples. Now I don't know what the time course is. So I think if you have active disease it's likely that you'd have an increase in IL-17, but nobody has the data. I don't know. So it would be nice to have samples from different time points with different drugs because again, the more I see of this, there're many different mechanisms for drug-induced liver injury, and this is not going to be the only mechanism. I need samples from several patients.

DR. BONKOVSKY: Herb Bonkovsky. Are there known functional polymorphisms that affect expression of IL-17?

DR. UETRECHT: Good question. I haven't a clue. The first paper I can find about Th17 cells was published in 2006. So this is fairly new. I've been worrying about autoimmunity for some time but it wasn't until I saw these Th17 cells that are associated with autoimmunity that I could postulate, and again this is hypothesis, a mechanism.

DR. VIERLING: Vierling, Baylor College of Medicine. Jack, that was outstanding, and you certainly set the stage for how you may be worried about a rechallenge event and the potential for immune memory. You mentioned several times the potential absence of memory T cells that could be mediators for cytotoxicity, such as CD8 T cells. I think it's important to

recognize that Nick Crispe's work about the tolerogenic mechanisms of the liver has shown that dendritic cells phagocytose debris generated by necrosis and apoptosis in the liver, migrate to peripheral lymph nodes, and present antigens to CD4 and CD8 cells that then migrate back to the liver. Those T cells contain memory populations. In contrast, but there is a mechanism for direct activation of naïve CD8 T cells within the liver that generates cytotoxicity but does not generate memory T cells, which may have important implications regarding rechallenge. In such cases you would expect rechallenge effects to look as if the drug was being given de novo, and you showed nice examples of such responses that did not trigger immediate response from a memory population. I think that that the phenomenon of direct hepatic activation of CD8 T cells may play an important role in the rechallenge risk.

DR. UETRECHT: And again, it bugs me and my students even more, that in these rats, they're genetically identical and their environment is identical and yet only about half of them get the disease. Why is that?

DR. SENIOR: Are they really identical?

DR. UETRECHT: No, not really.

DR. SENIOR: They're from an inbred strain but they're not identical. They're not cloned.

DR. UETRECHT: No, they're not cloned. And, in fact, it was Brown Norways that were used to sequence the rat genome, and they had to go a little bit further to get them identical, but they're awfully damn close.