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Biosketch

Dr. Uetrecht is Professor of Pharmacy and Medicine and the Canada Research Chair in Adverse Drug Reactions. He received his Ph.D. in organic chemistry at Cornell University in 1972, M.D. at Ohio State University in 1975 and did his internal medical residency at the University of Kansas Medical Center from 1975-1978. He completed his clinical pharmacology fellowship in 1981 at Vanderbilt University and then joined the faculty. He moved to the University of Toronto in 1985 and was the associate dean of pharmacy from 1994 to 1998. His research is focused on the mechanisms of idiosyncratic drug reactions.

Abstract: Inhibition of Immune Tolerance Unmasks DILI Potential

Little is known with certainty about the basic mechanisms of idiosyncratic DILI. Their unpredictable nature makes it very difficult to perform prospective mechanistic studies in humans. Attempts to develop animal models have, in general, used high doses, and even when toxicity was observed, the characteristics were very different from the DILI in humans. There is increasing evidence, e.g. HLA associations, positive lymphocyte transformation tests, anti-drug antibodies, etc. that most DILI is immune mediated, even in the case of drugs such as isoniazid in which the DILI was categorized as metabolic idiosyncrasy. We had tried for decades to develop animal models of DILI and other idiosyncratic drug reactions by stimulating the immune system through toll-like receptors. Even immunizing animals with drug-modified hepatic proteins and adjuvant prevented the mild delayed onset liver injury that would otherwise occur, and it also led to an increase in Tregs and myeloid derived suppressor cells. Likewise, in humans it might be expected that inflammatory conditions such as inflammatory bowel disease would increase the risk of DILI, but in general it does not. It is likely that the default response is immune tolerance, and if that were not the case autoimmunity would be much more common. Two molecules involved in immune tolerance are PD-1 and CTLA-4. Recently a new class of anticancer drug was developed called checkpoint inhibitors: antibodies that block molecules such PD-1 and CTLA-4 and promote attack of tumors by the immune system. They can also lead to drug interactions because they increase the risk of idiosyncratic DILI. We have used PD-1-/- mice and anti-CTLA=4 antibodies to develop animal models of DILI. The first drug that we tested was amodiaquine because, unlike most drugs that cause DILI, it causes mild liver injury in wild type mice. However, this injury resolves despite continued treatment with the drug, a response called adaptation. However, when PD-1-/- mice were treated with amodiaquine + anti-CTLA-4 they developed more severe delayed onset liver injury characterized by piecemeal necrosis, and it did not resolve with continued treatment, although the animals did not develop liver failure. We went on to study other drugs including isoniazid and nevirapine and found that blocking PD-1 and anti-CTLA-4 also unmasked the ability of these drugs to cause DILI in mice, and it also differentiated troglitazone from pioglitazone. Another type of cell that is involved in immune tolerance is the myeloid-derived suppressor cells, and Lance Pohl showed that anti-DR-1 antibodies, which deplete these cells, unmasked halothane-induced liver injury. We found that these antibodies also increased amodiaquine-induced liver injury, but instead of being synergistic with the checkpoint inhibitors, these antibodies were actually antagonistic, i.e. the combination prevented the more severe liver injury that occurred with either intervention alone. Clearly immune tolerance is complex, but the ability to modulate immune tolerance now allows us to rigorously study the mechanisms of DILI and potential interactions with other drugs.
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