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Biomarkers differentiate drug-induced liver injury from other liver injury: PONDER study

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Background and Aim: Drug-induced liver injury (DILI) is a known complication of volatile anesthetic (VA) agents, and, despite being rare, DILI can be serious. One mechanism of VA-DILI occurs via interleukin 4 (IL-4)-driven upregulation of cytochrome P450-2E1, leading to the formation of drug metabolites (haptens) that trigger IL-4-driven antigen-specific T cells and autoantibodies. Our group has developed biomarkers for liver injury and have examined this in patients before and after VA exposure. The aim of this prospective study was to determine the early markers of VA-DILI.

Methods: We prospectively followed patients having a VA general anesthetic (sevoflurane and/or desflurane) and compared them with those who received regional or total intravenous anesthesia. Exclusion criteria were known liver disease or any episode of significant hypotension. Baseline data on patient demographics and comorbidities were collected, and blood was analyzed for liver biochemistry, macrophage activation markers (CD206, CD163), and IgG1 and IgG4 antibodies to JHDN5 (the CYP2E1 epitope) and trifluoroacetyl (TFA), the VA drug hapten. Follow-up blood samples were taken 48 h postoperatively and compared with baseline results. DILI was defined as an alanine aminotransferase (ALT) level greater than two times the upper limit of normal (ULN) and post-review agreement by an expert panel, taking into account the pattern of liver function test result derangement and intraoperative events.

Results: Of 229 patients recruited, 16 developed an ALT level $> 2 \times$ ULN. Twelve were considered likely to have VA-DILI, including four with an ALT rise $>3 \times$ ULN. There was a trend to associate VA-DILI with obesity (RR, 2.98; $P = 0.063$); however, the association with dyslipidemia (RR, 1.47; $P = 0.72$), male sex (RR, 1.18; $P = 0.76$), history of atopy (RR, 1.16; $P = 0.79$), and heavy ethanol consumption (RR, 1.09; $P = 0.89$) was not statistically significant. Prior VA exposure was not a risk factor (RR, 0.89; $P = 0.83$). There was a rise in CD206 and decline in CD163

from baseline in all patients. However, in the patients with VA-DILI, the levels were significantly different from all other groups. TFA IgG1 and IgG4 antibodies were elevated in the VA-DILI group when compared with controls.

Conclusion: Recognizing that our results may be skewed by our cohort, this work suggests the known immunological pathway mediated by IL-4 in response to an injury: rise in CD206 to stimulate an inflammatory response, and decrease in CD163 to modulate the response. The increase in TFA IgG1 and IgG4 antibodies in the VA-DILI group is consistent with metabolism and the heightened immune response in those who develop DILI. At this early juncture, JHDN5 IgG4 autoantibodies were not detected. Ongoing work is looking at other DILI, and how these markers can be used in DILI.