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RESPONSE TO LETTER TO THE EDITOR

Response by Brunham et al to Letter Regarding Article, "Inhibition of Cholesteryl Ester Transfer Protein Preserves High-Density Lipoprotein Cholesterol and Improves Survival in Sepsis"

Liam R. Brunham, MD, PhD; Mark Trinder, MSc; Patrick C.N. Rensen, PhD; John Boyd, MD

In Response:

We thank Quintão and Cazita for their interest in our recent publication.¹ They suggest that cholesteryl ester transfer protein (CETP) may play a protective role in sepsis based on studies in mice transgenic for human CETP that showed improved survival after lipopolysaccharide administration or polymicrobial sepsis² and the proposed ability of CETP to enhance the binding of lipopolysaccharide to high-density lipoprotein (HDL). However, a recent study questioned whether CETP has lipopolysaccharide-binding activity and reported the opposite effect, namely that human CETP worsens survival in mouse models of sepsis.³ In humans presenting with sepsis, CETP activity is decreased, presumably in an attempt to preserve HDL levels.⁴ Carriers of a gain-of-function variant in the CETP gene (rs1800777) are unable to downregulate CETP activity during sepsis, have very low HDL, and have an increased risk of organ dysfunction and death.⁵ Mendelian randomization suggests that low HDL cholesterol attributable to genetically increased CETP activity is associated with worse survival from sepsis,⁵ and a polygenic score for reduced CETP activity is associated with improved survival from sepsis.¹ Last, pharmacological inhibition of CETP in humanized APOE*3-Leiden.CETP mice preserves HDL cholesterol levels and improves survival from sepsis, an effect that is dependent on the presence of CETP.¹ We believe that these data are most consistent with a model in which elevated levels of CETP during sepsis lead to lower levels of HDL and a corresponding worse outcome. Nevertheless, we agree that additional work is needed to clarify the exact mechanisms by which both

CETP and HDL influence the host response to infection, which may lead to opportunities to therapeutically target HDL metabolism to treat sepsis.

ARTICLE INFORMATION

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Disclosures

None.

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