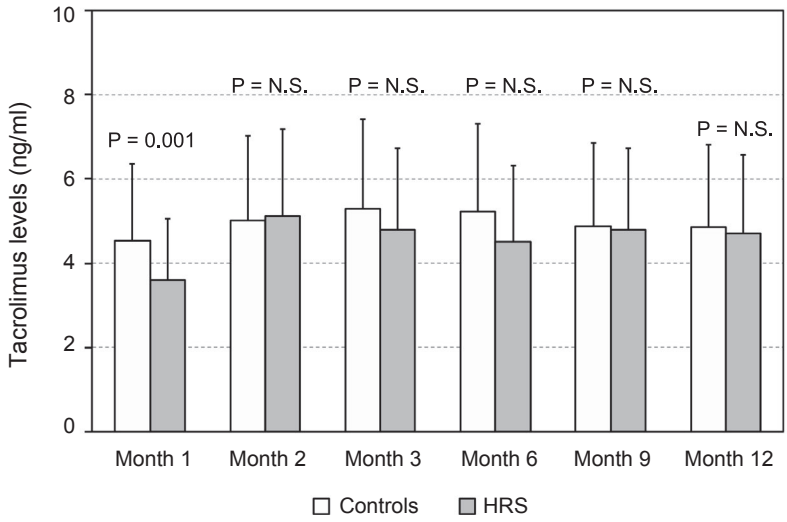

FIG. 1. Trough levels of tacrolimus during the first year after LT in patients with or without HRS. Abbreviation: N.S., not significant.

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Potential conflict of interest: Dr. Piano advises Mallinckrodt.

Letter to the Editor: Entecavir Treatment Restores the Anti-HBV Immune response?

TO THE EDITOR:

With great interest, we read the manuscript by De Pasquale et al.[1] They convincingly showed that dendritic cells (DCs), generated *in vitro* from monocytes of patients with HBV, have a detrimental effect on the function of natural killer (NK) cells, leading to the insufficient anti-HBV response observed in patients with chronic HBV. However, many years ago, we conducted a similar study.[2] In our study, we did not use monocyte-derived DCs, but only *ex vivo* isolated blood dendritic cell antigen 1–positive (BDCA1+) DCs, and examined the DC–NK interaction in a larger and prospectively designed cohort study of 39 patients with HBV and 16 healthy controls. Given the complexity of these type of studies, we were pleased to learn that the study by De Pasquale et al. supported our earlier findings.

In one challenging experiment of our earlier study, we co-cultured pretreatment NK cells with BDCA1+ DCs isolated from the same patient before and during 6 months of entecavir treatment. We observed that antiviral therapy enhanced the production of multiple DC-derived cytokines (including IL-12p70), and consequently improved the anti-HBV-associated DC–NK cell function. Our *ex vivo* experiments clearly show, as in the current study by De Paquale

et al., that altered DC function in patients with chronic HBV leads to impairment of NK cell activity, which can be reversed by antiviral treatment.

We were intrigued to read that a soluble factor in the serum of patients with chronic HBV impaired co-cultured DC function, something not observed when using sera from entecavir-treated patients. De Pasquale et al. suggested a role for IL-10; however, many cytokines are known to respond to entecavir treatment. For instance, during entecavir treatment, plasma levels of immune-suppressive TGF-β1 and pro-inflammatory IL-17 and IL-23 gradually decrease, while IL-4-stimulating and DC-stimulating interferon-γ increase.[3] We conclude that the soluble serum factor that modulates the DC–NK cross talk leading to impaired NK cell activity is not just IL-10, but rather a complex serum cytokine milieu, deserving of better characterization.

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REPLY:

We received with pleasure the commentary on our recent publication and wish to thank the authors for appreciating our work.[1]

With the aim of better clarifying the experimental settings and the purpose of our study, we will here briefly point out a few issues that we feel need some precision.

Differently from what is stated in the correspondence by Beudeker et al., we did not derive dendritic cells (DCs) from the monocytes of patients with HBV but rather exposed both monocyte-DCs and *ex vivo* isolated BDCA1$^+$ DCs to either HBV or serum of patients who were chronically infected, and we comprehensively investigated possible interactions of HBV-exposed DCs with natural killer (NK) cells. In addition, as a corollary, we performed confirmatory experiments with BDCA1$^+$ DCs and NK cells directly isolated from patients with chronic HBV.

Therefore, our data had not been previously generated and actually extend and corroborate a series of former reports regarding defective innate immune responses induced by HBV. Actually, by planning this study, we were particularly focused in a specific topic, i.e., elucidating DC/NK cross-talk, a bidirectional cell activation we formerly pioneered in the human system, in the presence of HBV.

A foremost finding in our current study is that not only DC impairment induced by HBV can affect NK functions but also that, in turn, the missed NK cell activation during the cross-talk results in a further impairment of DC activation, including their ability to assemble a suitable immunoproteasome and therefore efficiently present antigens during the subsequent adaptive immune response. In a similar bidirectional interaction, HBV-exposed DCs can shelter themselves from NK attack, allowing DCs to recirculate in an immature and potentially tolerogenic state. Our current data provide an additional interesting explanation for the diffuse immunocompromised state frequently occurring in patients with chronic HBV.

Regarding the mechanism employed by HBV to affect DC functions, we agree that a complex serum cytokine milieu, not just IL-10, probably contributes