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Be Aware of the Dog: Tacrolimus Usage and Chronic Hepatitis E Virus Infections

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Tacrolimus is an immunosuppressive drug that is used to prevent and treat organ rejection in liver, heart, and kidney transplant recipients.[1–3] As a macrolide calcineurin inhibitor, it specifically disrupts T cell signal transduction and activation by inhibiting the transcription and release of cytokines, notably interleukin-2, as well as c-myc, interleukin-3, tumor necrosis factor alpha, and interferon-gamma in T cells. Importantly, tacrolimus also dampens adaptive immune responses to viruses by downregulating T cell activation and has recently been suggested, along with other factors, to be associated with the risk of developing chronic hepatitis E (CHE).[4] In this issue of Kidney International Reports, Leon-Janampa *et al.*[5] conducted a retrospective clinical study involving a total of 2341 kidney transplant recipients (20 of whom were patients with CHE) with the primary aim of investigating the association between clinical and viral factors and the risk of CHE[5] (Figure 1).

Hepatitis E virus (HEV) is a single-stranded positive-sense RNA virus and the major causative agent of acute viral hepatitis in humans worldwide. Annually, HEV accounts for approximately 20 million infections worldwide, leading to about 3.3 million symptomatic cases and resulting in 44,000 to 70,000 deaths.[6] HEV infections are usually self-limiting and asymptomatic in immunocompetent individuals. However, in about 47% to 66% of immunosuppressed patients, HEV replication can persist beyond 3 months after HEV infection, causing CHE, thus increasing the risk of severe fibrosis and cirrhosis.[7] The management of CHE in these patients typically involves the off-label use of ribavirin, which achieves a sustained virological response in 81% of cases. This treatment is particularly crucial when reduction of immunosuppression—a strategy effective in achieving viral clearance in 30%[4] of cases—is ineffective or not applicable.[8]

So far, recent studies have identified several predictors of chronic infection, including time between the last episode of acute rejection and HEV, time since transplant, low leukocyte and platelet count, low CD2-positive, CD3-positive, and CD4-positive cell counts, as well as low alanine transaminase and aspartate aminotransferase levels at diagnosis of HEV infection.[9,S1] Importantly, the use of tacrolimus over cyclosporin A appears to be a crucial independent predictive factor for the development of chronic hepatitis.[4,S2] Yet, factors that contribute to the development of chronic infection in immunosuppressed individuals are still incompletely understood. In line with previous studies,[4] Leon-Janampa *et al.*[5] observed about 74 % CHE in kidney transplant recipients infected with HEV.[5] By retrospectively analyzing patient characteristics, they also underscore the significant risk posed by high tacrolimus trough concentrations at the time of diagnosis in fostering CHE among kidney transplant recipients (9.2 vs. 6.4 ng/ml, $P = 0.04$). However, they also state that these observations need to be further explored in other solid organ and hematopoietic stem cell transplant patients with CHE.[5]

Similar to the effects of tacrolimus, high intrahost genetic heterogeneity, particularly within the polyproline region and the macro domain of the *ORF1* gene, has been linked to the progression to CHE.[S3,S4] Leon-Janampa *et al.*[5] contributed to these findings by comparing and analyzing sequences from both the acute and chronic phases of HEV infection in kidney transplant recipients. Their study demonstrates notable genetic variability among hosts infected with HEV genotype 3. Furthermore, a longitudinal analysis of HEV genetic diversity identified 2 significant

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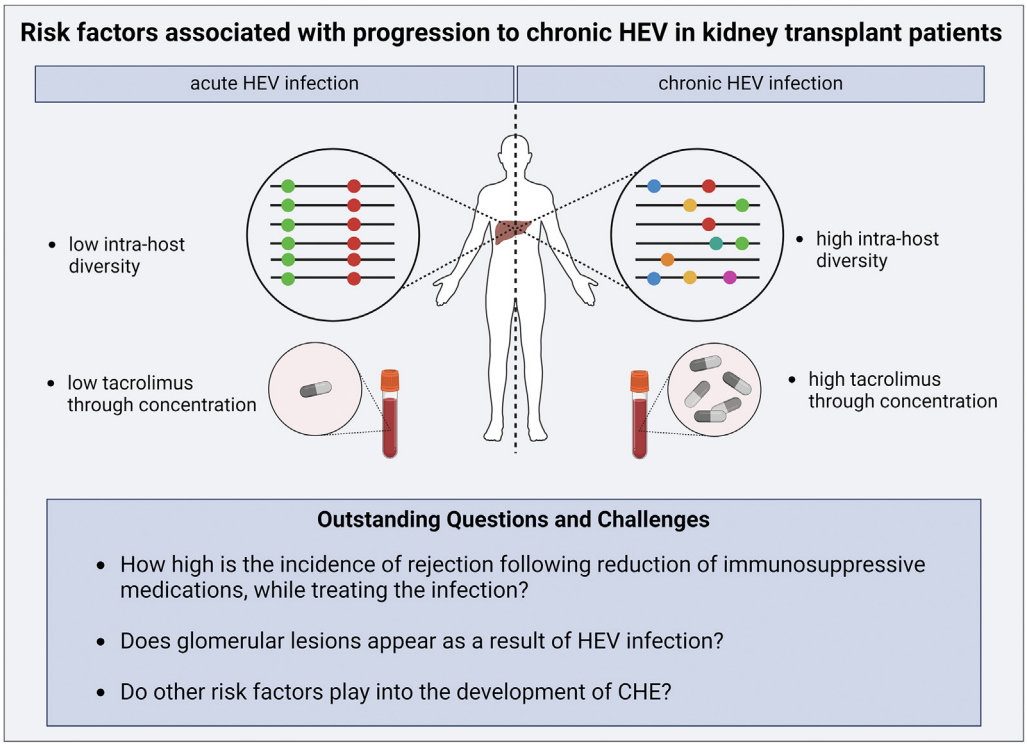

Figure 1. Risk factors associated with progression to chronic HEV in kidney transplant patients. Factors associated with progression to chronicity in kidney transplant recipients include high intrahost diversity and high tacrolimus through concentration. CHE, chronic hepatitis E; HEV, hepatitis E virus. Created with BioRender.com.

mutations, E749Q within the hypervariable region and L828I within the ADP ribose domain of *ORF1*, that were exclusively observed during the chronic phase of the infection. In addition, the study observed that most genetic alterations selected during HEV infection were distinctively compartmentalized between plasma and feces, highlighting the complex dynamics of viral evolution during CHE.

Although numerous questions persist regarding the emergence of CHE under immunosuppression, the work by Leon-Janampa *et al.*[5] highlights the association between tacrolimus use and the progression toward CHE in solid-organ transplant recipients, particularly those with kidney transplants. Given the European Association for the Study of the Liver guidelines, reducing immunosuppressive medications that target T cells is already a primary therapeutic approach for managing CHE. In situations where this strategy is feasible, opting for a low-dose tacrolimus regimen could potentially lower the risk of progressing to chronicity. This research underscores the significance of identifying key factors that contribute to the development of chronic hepatitis. Accurately predicting these factors is crucial for the clinical management of chronic HEV infection, enabling health care providers to identify patients at risk of not spontaneously clearing the virus. Such patients may significantly benefit from early intervention with ribavirin. This approach is vital for tailoring therapeutic strategies and improving outcomes for individuals with chronic HEV infection.

DISCLOSURE

All the authors declared no competing interests.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary References.

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