Commentary

Functional cure of chronic hepatitis B – predictable?

Wolfram Gerlich

Justus Liebig University Giessen, Institute of Medical Virology, National Reference Centre for Hepatitis B Viruses and Hepatitis D Viruses, Giessen, Germany

Chronic hepatitis B (CHB) infection is still a huge public health problem, although tremendous progress in prevention and therapy of this infection has been achieved in the last decades. Vaccination has reduced prevalence of CHB by more than 90 % in vaccinated young adults [1]. Therapy of the still very numerous existing cases of CHB in adults (estimated 257 million worldwide) with nucleos/tide analogs and/or interferon can suppress replication of HBV and progression of the liver disease. An open problem is, however, the achievement of a permanent cure of CHB allowing for safe termination of antiviral therapy. The HBV genome persists in the liver and continues to express its genes in spite of inhibited replication or active immune reactions. One of the key factors potentially leading to suppression of HBV gene expression is an immune defense against HBV antigens by activated T cells. The main target of the T cells is the HBV core antigen (HBcAg), but the most sensitive marker of HBV gene expression is the HBV surface antigen (HBsAg) in the serum. Loss of serum HBsAg during CHB is generally accepted as marker of a so-called “functional cure” indicating an efficient immune response against HBV genome expression [2-4].

The article from Shue Xiong and colleagues in this issue of EBioMedicine [5] followed the kinetics (i.e., “longitudinal”) of many markers for T cell activity in blood mononuclear cells of 172 CHB patients before, during and after the loss of HBsAg for periods up to 60 weeks. Most patients, but not all, had received antiviral therapy.

HBsAg loss during CHB is a slow process which cannot be accelerated very much by therapy with nucleos/tide therapy. Consequently, a weakness of the study is that 141 of the 172 patients retained HBsAg during the follow-up and only 6 showed HBsAg loss. As supplement, the study included 25 patients in whom HBsAg loss had been early phases of HBsAg elimination, and appeared later in the blood.

Liver samples, were, however, not available for the study.

Loss of serum HBsAg during CHB is a slow process which cannot be accelerated very much by therapy with nucleos/tide therapy. Consequently, a weakness of the study is that 141 of the 172 patients retained HBsAg during the follow-up and only 6 showed HBsAg loss. As supplement, the study included 25 patients in whom HBsAg loss had been observed in the years before. Furthermore, the authors followed the HBsAg concentration in 19 patients without HBsAg loss and correlated its “rapid decrease” with the T cell parameters. The authors summarize their data on T cells as follows: “Collectively, these data show that the activated phenotype of T cells is associated with the intensities of HBsAg reduction and HBV-specific T cell responses during the course of rapid HBsAg decrease and loss.” This is important and supports some current concepts for future immune stimulatory therapies, e.g., with a therapeutic vaccine [6]. The study also confirmed the old observation that therapy with pegylated interferon alpha induces activation of T cells and HBsAg loss in many patients months after the therapy. Surprising is the finding that the marker of T cell exhaustion PD1 was enhanced in patients with therapy. The authors mention that PD1 may also be a marker T cell survival which finally may result in the formation of T memory cells and subsequent immune responses.

The most universal marker of T cell activation seemed to be expression of HLA-DR which was found elevated in patients with rapid HBsAg decrease. Consistently, patients who developed anti-HBs after HBsAg loss had also enhanced HLA-DR. The findings on the HBcAg-specific CD8+ T cell response are somewhat puzzling. It was virtually absent in patients with constant HBsAg levels as expected, but it seemingly remained weak even during rapid HBsAg decrease. In contrast, the loss of HBsAg was accompanied or followed by enhanced HBcAg-specific CD8+ T cell responses. Possibly, the HBcAg-specific T cells were retained in the HBV-infected liver during the early phases of HBsAg elimination, and appeared later in the blood.

Liver samples were, however, not available for the study.

A mainstay for the long-term prognosis of CHB is the HBsAg level. The study followed mainly patients with low levels of HBsAg (<1000 IU/mL) which were already close to HBsAg loss. Many of the tested markers of the global T cell activity were significantly correlated with the loss of HBsAg (Table 2), but the best predictors of HBsAg loss were the quantity of HBsAg itself and the percentage of HLA-DR+ CD8+ T cells. Combination of quantitative HBsAg with this or further T cell markers may improve the prediction, but considering the high technical effort of the T cell profiling, other approaches may be considered.

According to EASL, HBV infection may proceed through different phases from the highly replicative, quasi-immune tolerant to the occult, HBsAg negative phase [4]. The distinction between HBsAg positive or negative at a limit of detection of 0.1 IU/mL appears somewhat arbitrary. There are far more sensitive HBsAg assays [7]. The transition from the inflammatory chronic hepatitis B to the asymptomatic inactive carrier state with lower but still present HBsAg is...
much more relevant than reaching the so-called functional cure which is in fact a form of occult HBV infection. The results of the study are very interesting concerning the T cell-related mechanisms of immune control of CHB, but the focus on the period of the last months before and after undetectability of HBsAg impairs its practical usefulness.

There are many other serological markers of HBV activity or immunity than a qualitative HBsAg result at the limit of analytical sensitivity. One unjustified simplification in the diagnosis of HBV is the neglect of the middle and large HBs proteins with their preS2 and preS1 domains. Using rather simple quantitative ELISAs for preS1 and 2 antigens in serum, the natural course of CHB [8] or the outcome of antiviral therapies including interferon [9] could be rather dependably predicted. Irrespective of these remarks, the study gives interesting insights to the role of T cells in controlling HBV infection. Future, similar in-depth studies of immune cells in CHB should also be devoted to the role of B cells.

**Declaration of Competing Interest**

The author declares no competing interests.

**References**

[1] Global Hepatitis Report 2017. Geneva: World Health Organization; 2017 Licence: CC BY-NC-SA 3.0 IGO.

[2] Lok AS, Zoulim F, Dusheiko G, Ghany MG. Hepatitis B cure: From discovery to regulatory approval. J Hepatol 2017;67:847–61.

[3] Cornberg M, Lok AS, Terrault NA, Zoulim F. EASL-AASLD HBV Treatment Endpoints Conference Faculty. Guidance for design and endpoints of clinical trials in chronic hepatitis B - Report from the 2019 EASL-AASLD HBV Treatment Endpoints Conference Faculty. J Hepatol 2020;72:539–57. doi: 10.1016/j.jhep.2019.11.003.

[4] European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B 464 virus infection. J Hepatol 2017;67:370–98. doi: 10.1016/j.jhep.2017.03.021.

[5] Xiong S, et al. Longitudinal characterization of phenotypic profile of T cells in chronic hepatitis B identifies immune markers associated with HBsAg loss. EBioMedicine 2021;69 July. doi: 10.1016/j.ebiom.2021.103464.

[6] Cornelius C, Scheneweis K, Georgi F, Weber M, Niederberger V, Zieglmayer P, Niespodziana K, Trauner M, Hofer H, Urban S, Valenta R. Immunotherapy With the PreS-based Grass Pollen Allergy Vaccine BM32 Induces Antibody Responses Protecting Against Hepatitis B Infection. EBioMedicine 2016;11:58–67 Sep. doi: 10.1016/j.ebiom.2016.07.023.

[7] Deguchi M, Kagita M, Yoshioka N, et al. Evaluation of the highly sensitive chemiluminescent enzyme immunoassay “Lumipulse HBsAg-HQ” for hepatitis B virus screening. J Clin Lab Anal 2018;32:e22334. doi: 10.1002/jcla.22334.

[8] Pfefferkorn M, Böhm S, Schott T, Deichsel D, Bremer CM, Schröder K, et al. Quantification of large and middle proteins of hepatitis B virus surface antigen (HBsAg) as a novel tool for the identification of inactive HBV carriers. Gut 2018;67(11):2045–53 Nov. doi: 10.1136/gutjnl-2017-313811.

[9] Pfefferkorn M, Schott T, Böhm S, Deichsel D, Felkot C, Gerlich WH, Glebe D, Wat C, Pavlovic V, Heyne R, Berg T, van Bommel F. Composition of HBsAg is predictive of HBsAg loss during treatment in patients with HBeAg-positive chronic hepatitis B. J Hepatol 2021;74(2):283–92 Feb. doi: 10.1016/j.jhep.2020.08.039.