How Durable Is Functional Cure (Hepatitis B Surface Antigen Loss) in Patients With Chronic Hepatitis B Treated With Current Antivirals?

The achievement of hepatitis B surface antigen (HBsAg) loss and its durability off treatment are of paramount importance for current and future anti-hepatitis B virus (HBV) strategies. Because HBsAg loss is a rare event, multicenter studies and pooled analyses may be instrumental, as demonstrated by Lok et al.\(^1\) in this issue of Hepatology Communications.

Among 1,381 patients with chronic hepatitis B (CHB) treated with either tenofovir disoproxil fumarate (TDF) monotherapy for up to 10 years or pegylated interferon (PEG-IFN)-containing regimens for up to 1 year and enrolled in three international trials, 55 (3.9%) had confirmed HBsAg loss. Of these 55 patients, 29 received TDF monotherapy and 26 were treated with PEG-IFN with or without TDF; 45 (82%) had confirmed and sustained HBsAg loss and 10 seroreverted to HBsAg positivity during a median follow-up period of 96 (46-135) weeks after first HBsAg loss. The risk of HBsAg seroreversion was lower if HBsAg loss was sustained through off treatment. Overall, antibody to hepatitis B surface antigen (anti-HBs) seroconversion was observed in 43 (78%) patients who achieved HBsAg loss, with similar rates in patients treated with nucleos(t)ide (NUC) and PEG-IFN (79% vs. 77%, respectively).

This study is important for several reasons. First, in a well-characterized population followed for many years, the rate of drug-induced HBsAg loss is indeed a rare event (<5%). Second, the study describes carefully the durability of HBsAg loss and the probability of anti-HBs seroconversion over time. Third, the combination of TDF and PEG-IFN increased the rates of HBsAg loss compared to TDF monotherapy.

As far as the probability of HBsAg during antiviral treatment for HBV is concerned, most studies agree that this is a rare event that is possibly related to duration of NUC therapy, baseline HBsAg levels, disease severity, and phases of the natural history of HBV, among other predictors. These disappointingly low rates of HBsAg loss relate mainly to the mechanism of action of NUC therapy, which does not directly interfere with viral antigen production or secretion. One might ask why this endpoint, HBsAg loss, is so...
relevant as patients on long-term term NUC have excellent prognosis and outcomes while remaining HBsAg positive. From a practical viewpoint, the clearance of HBsAg is the best and safest stopping rule for NUC therapy. Biologically and virologically speaking, HBsAg loss correlates with a reduced number of infected liver cells and/or silencing of covalently closed circular DNA. In clinical terms, the risk of hepatocellular carcinoma may further decline after functional cure in patients with CHB but probably not in those with cirrhosis. All in all, there is a strong rationale for pursuing strategies aimed to accelerate HBsAg decline and foster HBsAg loss, including the combination of NUC and IFN, which may work, albeit in selected patients and only at the price of significant side effects.

In terms of durability of spontaneous and treatment-induced HBsAg loss, the present study is mainly confirmatory of other studies. HBsAg loss is a rare event, but once achieved it is stable and long lasting in most patients and is frequently associated with anti-HBs seroconversion. Whether production of anti-HBs is associated with immunologic or clinical advantages is still unclear, although the risk of HBV seroreversion during immunosuppression is lower in patients who are HBsAg negative/anti-HB core with high anti-HBs titters.

The topic covered by this study is relevant not only for current therapeutic strategies but also for new therapeutics under preclinical and clinical development. What is the likelihood of HBsAg loss with new therapeutics and the durability of these virologic responses? How do the results achieved with current anti-HBV strategies compare with what could be achieved by new treatment strategies? To set the stage for this new clinical setting, new definitions of virologic responses have been proposed by a joint European Association for the Study of the Liver and American Association for the Study of Liver Diseases working group of experts in the field. The now popular terms “functional cure” and “partial cure” refer to off-treatment HBsAg loss, with or without anti-HBs seroconversion, plus undetectable HBV DNA (functional cure) and off-treatment HBsAg positivity with undetectable HBV DNA (partial cure). To avoid any confusion, the term HBsAg loss overlaps with the term functional cure.

Combination therapies with new therapeutics endowed with different mechanisms of action, for example, direct antivirals plus immunotherapies, may provide better functional cure rates with short-term finite treatment courses compared to what can currently be achieved. However, given the new mechanisms of action of many of these combinations as well as the faster kinetics of HBsAg decline that can be hypothesized for some of these compounds and the new immunoactivation pathways they target, the durability of functional cure with these new antiviral approaches should not be taken for granted. Specific studies should tackle this topic because this event is indeed very stable over time even though current therapies induce HBsAg loss in few patients. We are not aware of any new experimental short-term finite antiviral strategy that has shown high rates of functional cure, with the exception of the nucleic acid polymer (NAP) study, a 48-week TDF + PEG-IFN + NAP combination study in which high rates of HBsAg loss, anti-HBs production, and alanine aminotransferase (ALT) normalization were observed in patients with CHB who were treatment naive. Interestingly, these excellent virologic responses were sustained off therapy in most of the patients. Although very promising, these results should be taken with caution because the study had some significant limitations, including the need for IFN administration, the intravenous administration of NAP, and the occurrence of significant ALT flares.

In conclusion, this study sheds new light on the durability of HBsAg loss in patients with CHB treated with TDF or in combination with PEG-IFN, findings that are in line with what has been described in other studies and during the natural history of HBV. The fact that the durability of NUC- and IFN-induced HBsAg loss mimics the durability of spontaneous-induced HBsAg clearance suggests that similar mechanisms may play a role in these two different clinical scenarios. It remains to be seen whether new antiviral strategies based on the combination of direct antivirals and immunomodulators may be successful in combining the advantages of short-term finite therapy with high rates of durable functional cure.

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