THE FORUM
For Collaborative Research℠

Management of Finite Treatment for CHB: similar and different concerns with new drug classes

Working Group Update

HBV Forum 10

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HBV Forum

- The HBV Forum convened a webinar in July 2021
- Then formed working group discussions to address how and when to stop finite therapy for demonstration of sustained off-treatment efficacy and safety responses.
- Participants included leading experts in academia, clinical practice, pharmaceutical companies, patient representatives and regulatory agencies.
- Writing group was formed to outline areas of consensus within our multi-stakeholder group for stopping finite therapies in chronic Hepatitis B investigational studies, including trial design, patient selection, outcomes, biomarkers, pre-defined stopping criteria, pre-defined retreatment criteria, duration of investigational therapies, and follow up after stopping therapy. Future research of unmet needs were discussed.
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Chronic Hepatitis B Finite Treatment: similar and different concerns with new drug classes

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on behalf of the HBV Forum Stopping Finite Therapy Working Group

Area of interest	Consensus
Design of studies	• Designing new finite duration therapeutic regimens to achieve functional cure is complex due to the differing MOAs and heterogeneity based on patient characteristics • Early patient input will enhance acceptability of drugs/trial design
Patient selection	• Initial studies of finite and curative investigational therapies should focus on enrollment of patients without cirrhosis with minimal fibrosis for safety of trial participants
Outcomes	• Functional Cure: HBsAg loss +/- anti-HBs and HBV DNA below the LLOQ sustained for at least 24 weeks off all treatment. • Partial cure: HBsAg positive and HBV DNA <LLOQ sustained for at least 24 weeks off all treatment: include as a secondary endpoint.
Biomarkers	• HBsAg level at EOT: the most promising biomarker associated with lower chance of disease relapse and higher likelihood of HBsAg loss after stopping therapy. • EOT HBsAg <100 IU/mL, HBcrAg <4 $\log_{10}$ U/mL and HBV RNA negativity may improve the accuracy to identify patients who could benefit from stopping treatment

Area of interest	Consensus
Pre-defined stopping criteria	• Pre-defined stopping criteria should include low or negative HBsAg, negative HBV DNA and normal or slightly elevated ALT.
Pre-defined retreatment criteria	• The threshold for retreating study participant needs to be carefully pre-defined in the protocol based on latest data to allow adequate time to see an off-treatment response while ensuring patient safety. • Off treatment monitoring must be frequent (2-4 weeks) with rapid turnaround of liver tests and virologic (HBV DNA, qHBsAg) tests
Duration of investigational therapies	• The duration and complexity of any treatment regimens should be acceptable to the patient population.
Follow up after stopping therapy	· Patients should be followed up for more than 24 weeks, at least 48 weeks. · Long term follow-up studies are recommended to assess durability or response, additional HBsAg loss and late relapse.

Area	Specific Future need
Definitions	Uniform definitions of cure (functional, partial) and inactive state as well as biochemical and virological relapse should be used across trials
Predictors	Predictors of success should be systematically evaluated in all trials including those with NrtI discontinuation and should include qHBsAg and other markers, such as HBV RNA and HBcrAg
Stopping criteria	Different stopping criteria may need to be developed for regimens depending on whether different MOA (viral inhibitors and/or immune modulators) are incorporated in a treatment regimen.
Source of HBsAg	There is a major need to be able to differentiate the source of HBsAg between iDNA and cccDNA

Area	Specific Future need
Immunology	• No immunological biomarkers predict functional cure currently. • Immune biomarkers need to be tailored to reflect the MOA of different agents and identify immune system targets: prioritizing the analysis of HBsAg-specific T and B cells for drugs targeting HBsAg; ensuring analysis of liver immunity if using a liver-targeted agent like LNA oligonucleotide targeting PD-L1. • New methods for measuring restoration of HBV-specific immune control are needed
Trial samples	• All trials should include banked serum/plasma, and PBMCs at pre-treatment and end of therapy at a minimum to screen and evaluate potential immune and virologic markers. • Pathogenesis-focused trials should include fine needle aspiration and liver biopsy in addition
Drug Resistance	Assessing for resistance against all drugs in the regimen will be an important consideration for participants with lack of on-treatment response and/or relapse after stopping a finite treatment regimen

Thank You!