



HBV FORUM: STOPPING NUCs IN DRUG DEVELOPMENT

Wednesday, July 14, 2021

12:00 – 2:00 pm EST

Presenters:

- Jessica Weber, *Forum for Collaborative Research*
- Grishma Hirode, *University of Toronto*
- Maria Beumont-Mauviel, *Janssen*
- Luisa Stamm, *Assembly Biosciences*
- Anna Maria Geretti, *Roche*
- Susanna Tan, *Gilead Sciences, Inc.*
- Poonam Mishra, *FDA*
- Stephanie Buchholz, *BfArM*
- Kosh Agarwal, *King's College London*
- Marion Peters, *Northwestern University*

Moderators:

- Harry Janssen, *University of Toronto*
- Nezam Afdhal, *Beth Israel Deaconess Medical Center*

Presentations

Presenter: Jessica Weber, *Forum for Collaborative Research*

Title: Introductions and Reminders

Slides: <https://bit.ly/3Enz7OO>

Overview of the webinar:

- This webinar will feature an overview of stopping NUCs in current clinical practice, presentations on industry strategies for stopping NUCs, regulatory perspectives on trial designs, a discussion how to move forward from the academic perspective, and an audience Q&A

- This is the first in a series of HBV Forum webinars in 2021. We will also have webinars focused on therapeutic vaccines and treatment indications based on the science
- The Forum will also be hosting a webinar on Translating Real World Data into Real World Evidence

Participation:

- The Forum restricts industry participation to experts with the necessary scientific knowledge with a clear commitment to advancing the therapeutic field related to HBV.
- Presentations, discussions, comments, and questions are not for attribution. Participants speak as individuals and express views that may not represent those of their organizations.

Overview of the HBV Forum

- What: a platform for ongoing multi-stakeholder dialogue to identify barriers, prioritize research and identify solutions to accelerate therapeutic development for HBV
- How: provide a neutral, independent, safe space for discussion and deliberation across stakeholder groups
 - Focus on developing consensus, increasing synergy and collaboration, and reducing duplication and uncertainty
 - Ongoing working group activity throughout the year anchored by larger project events
 - Active & engaged participation

Presenter: Grishma Hirode, *University of Toronto*

Title: Overview of Stopping NUCs in Clinical Practice

Slides: <https://bit.ly/39aaaIf>

Current Clinical Practice

- The majority of Hepatitis B virus patients right now require infinite nucleoside analog therapy
- Main goals of nucleos(t)ide analogue (NUC) therapy for chronic hepatitis B (CHB) patients:
 - Long-term HBV DNA suppression
 - HBeAg loss, with or without anti-HBe seroconversion, in HBeAg positive CHB patients
 - ALT normalization
 - HBsAg loss, with or without anti-HBs seroconversion → optimal endpoint!
 - Improve survival and quality of life by preventing disease progression and HCC
- Current guidelines:

- The Asian Pacific Association for the Study of the Liver (APASL) 2016
- The European Association for the Study of the Liver (EASL) 2017
- The American Association for the Study of Liver Diseases (AASLD) 2018

Stopping NUC Therapy

- Over the past few years, finite NUC therapy has been proposed as an alternative to long-term therapy, but the safe discontinuation of NUCs is still controversial
- Benefits of Stopping NUC Therapy
 - Life-long therapy not required, which may result in lower costs for the patients and may eliminate issues with patient non-adherence and non-compliance to the NUC
 - Currently long-term side-effects beyond ten years for many of the newer, more potent NUCs are not known
 - HBsAg loss on NUC therapy is rare; recent studies show that the rate of HBsAg loss off NUCs is relatively high
 - This is by far the most compelling reason in favor of stopping NUC therapy
 - However, there is a lot of heterogeneity between studies
- Cons of Stopping NUC Therapy
 - NUCs are cheap in most regions, safe and effective, improve long-term outcomes, and monitoring patients on this therapy is simple
 - Thus far, there have been no predictors of response after NUC withdrawal that have been well established. This means that strict surveillance is needed after stopping, which may result in higher patient costs, and deviations or non-compliance to the monitoring plan is far more dangerous off-therapy compared to on-therapy
 - While many of the patients who did not achieve HBsAg loss may remain off therapy, viral suppression after stopping therapy may not be as effective as on-therapy and other benefits such as improvements in fibrosis may be lost
- As a result of the many conflicting views and a lack of sufficient evidence, there are quite a few differences in stopping criteria

Stopping Guidelines

- Stopping Guidelines for HBeAg positive patients
 - The ideal endpoint is HBsAg loss
 - In the absence of HBsAg loss, all three guidelines agree that patients can be stopped following HBeAg seroconversion after 12 months of consolidation and undetectable HBV DNA
 - While EASL and AASLD do not recommend stopping therapy in cirrhotic patients, APASL guidelines say cirrhotic patients may be stopped but only with a very carefully outlined monitoring plan
- Stopping Guidelines for HBeAg negative patients

- The ideal endpoint is HBsAg loss
- Per APASL, patients need to have had at least 12 months of consolidation or achieve surface antibody positivity in addition to HBsAg loss
 - In the absence of HBsAg loss, only APASL has clear guidelines
 - NUCs may be redrawn in non-cirrhotics, who have been on NUC therapy for at least 2 years and have undetectable HBV DNA on 3 separate occasions 6 months apart
 - EASL mostly recommends continued therapy for HBeAg(-) patients without HBsAg loss, and they do suggest that NUCs withdrawal may be considered in a select few patients, provided that they are non-cirrhotic, well-suppressed, and post-NUC monitoring can be guaranteed
 - AASLD recommends continued therapy in the absence of HBsAg loss for all HBeAg(-) patients unless there is a very compelling rationale

To date, there have been three randomized controlled trials comparing on and off therapy outcomes:

- RCT: FINITE Study (2017)
 - Included 42 mostly Caucasian, non-cirrhotic, HBeAg(-) patients who received tenofovir for at least 4 years with viral suppression for at least 3.5 years
 - The primary endpoint was HBsAg loss at 144 weeks, which was 19% in the stop arm and 0% in the continue arm
 - Looking at the plots for the two arms, we can see that although there was more HBsAg decline and higher HBsAg loss in the stop arm, HBV DNA was not as well suppressed and there were more ALT elevations and flares in the stop arm compared to the continue arm
 - This was the case despite it being a highly controlled cohort under strict observation
 - At the end of follow-up, 38% had re-started therapy and even though ALT flares, clinical relapse, and decompensation were reasons for retreatment, the final decision to restart therapy was at the discretion of the investigator
- RCT: TORONTO STOP Study (2019)
 - Included 67 mostly Asian patients, they were all non-cirrhotic and virally suppressed, HBeAg(-) patients who received either entecavir or tenofovir for at least one year prior to the screening point
 - Patients were randomized in a 2:1 ratio to either stop or continue, and followed for 72 weeks
 - The results showed no difference in HBsAg loss or HBsAg decline between the two arms at 72 weeks
 - HBV DNA suppression was more effective in the continue arm compared to the stop arm, with 91% having levels below 20 IU/mL compared to the 2.2% in the stop arm at 72 weeks
 - There were also more ALT elevations/flares in the stop group

- At the end of follow-up, 38% of those in the stop arm had been re-treated and patients seemed to respond well to re-treatment
- The final decision to restart therapy was at the discretion of the treating physician
- RCT: Stop-NUC Trial
 - The largest trial to date
 - Included 158 mostly cirrhotic HBeAg(-) patients who had received either entecavir or tenofovir as per guidelines with viral suppression for at least 4 years
 - Patients were randomly assigned to either stop or continue, with 79 patients in each arm
 - Study showed that the stop arm had relatively higher HBsAg loss at 96 weeks, particularly among patients with end of therapy HBsAg levels below 1000 U/ml
 - 14% had restarted therapy by the end of follow-up
 - In the absence of flares and decompensation, restarting therapy relied on physician discretion
- No patients decompensated or died in any of the trials. However, all three studies determined that close monitoring post-NUC withdrawal is crucial

Cohort Studies

- Most are relatively small studies or studies among HBeAg(-) Asian patients
- The reported incidence of HBsAg loss after stopping varies across studies. This is based on patient population, the criteria used for stopping or retreatment, and the local policies
- There is need for analysis on a global scale with a large sample size, while accounting for potential confounders
- RETRACT-B study
 - Set up as a large, global, multi-center retrospective cohort of chronic hepatitis B patients who have discontinued NUC therapy, with the aim to analyze outcomes following NUC withdrawal. Study protocol was presented at HBV Forum in 2019
 - In current analysis, we included virally suppressed patients who were HBeAg(-) at NUC withdrawal, and excluded any patients with co-infection, with an HCC diagnosis prior to stopping, or if they had received pegylated interferon therapy within a year prior to stopping
 - Right now, there are a total of 12 participating centers
 - Among the 1,556 patients who stopped NUC therapy, most were over the age of 50 and male, 88% were Asian and 11% were Caucasian, and most received entecavir prior to stopping and were HBeAg(-) at start of therapy
 - At NUC withdrawal, 12 had been previously diagnosed with cirrhosis, the mean HBsAg level was 2.6 logs, and the median ALT was 0.6 times the upper limit of normal
 - The overall cumulative incidence of HBsAg loss after NUC withdrawal was 3% at one year and reached 13% at 4 years after NUC withdrawal. On univariate analysis there was statistically significant differences in the rate of HBsAg loss by

- age, by race, by the NUCs received prior to stopping, and by end of therapy HBsAg levels
- On multivariable analysis, only differences by race and by end of therapy HBsAg levels remained significant
 - In the adjusted model, the rate of HBsAg loss was 6x higher among Caucasians compared to Asians, and 12x higher among patients with end of therapy HBsAg levels below 100 IU/mL compared to patients who were above that threshold
 - The four-year cumulative incidence of virological relapse was 83%, clinical relapse was 55%, ALT flare was 31%, and retreatment was 56%
 - 19 patients developed hepatic decompensation off therapy
 - the rate was higher among patients previously diagnosed with cirrhosis, and among start of therapy HBeAg(+) patients
 - 16 patients developed HCC after NUC withdrawal, with a cumulative incidence of 1% at 4 years off-therapy
 - 14 patients died among the total cohort

What do we know about flares after stopping?

- We have some evidence that the risk of severe ALT flares after NUC withdrawal may be related to the severity of virological relapse, and that an ALT flare is not necessarily related to HBsAg loss
- If left untreated, may lead to complications and/or death
- Left graph: effective flare (host-dominating)
 - HBsAg levels and HBV DNA are elevated before the ALT peak, and subsequently decrease following the peak along with ALT normalization to achieve remission. Retreatment can be withheld in such a case
- Right graph: ineffective flare (virus-dominating)
 - HBsAg levels and HBV DNA continue to remain high, along with elevated ALT levels after the peak
 - Such a patient would benefit from timely re-treatment
 - Based on these results, they suggested more frequent monitoring when ALT is increasing, especially before and after the peak, and HBsAg quantification every 3 months after stopping. However, whether to wait and watch, whether to retreat, and if so, how long to wait are challenging decisions to make at the time the flare occurs, because we don't know which way the patient will go post-flare

What we know: Complications

- Only a handful of published studies; most are case reports or descriptive information
- Few studies comparing complication incidence on/off NUC therapy
- Rates can't really be compared across studies due to differences in baseline criteria; a large and long-term RCT is needed

What we know: Retreatment

- Many decisions now are based on physician discretion
- Virological relapse after stopping is almost universal, making it a poor criterion for retreatment
- None of the three guidelines outline any retreatment criteria
- Decision on when to retreat is crucial

Conclusions

- Most of what we know right now are from small, single-site studies that did not correct for selection or measurement bias
- Larger studies are from Asia
- Future direction
 - Better understanding of factors involved in pathogenesis
 - Identifying better biomarkers and predictors of response
 - Better understanding of post-NUC flares

Presenter: Maria Beumont-Mauviel, *Janssen*

Title: Considerations for stopping NA in HBV finite treatment

Slides: <https://bit.ly/2YXuavT>

Overview: Considerations related to stopping NA in Finite Treatment Duration Studies for Chronic HBV

- There are some guidelines, as Dr. Hirode already mentioned
- With the new mechanisms of action, it could be that the current guidelines are not appropriate. How do we move on from those principles and evaluate more liberal approaches so we can discontinue treatment in more patients and assess efficacy in terms of functional cure?
- Another consideration is the different mechanisms of action
- Will we need to incorporate a consolidation phase and consider a certain cut-off of HBsAg levels prior to discontinuing regimens? How low does this cutoff need to be? Will it be the same for regimens that are more a combination of immunomodulators?
- How long after we reach any of these thresholds can we then safely stop all treatment?
- Is it going to be necessary to add some biomarkers to the criteria we are using to stop treatment in order to identify patients that really can achieve functional cure and avoid the DNA rebound which is very frequently seen after we stop NUCs?
- Another consideration is the host and patient characteristics, and how these will influence which criteria to apply, including things such as age, race, and degree of fibrosis

NA Re-treatment Criteria

- This slide showed a schematic of guidelines in order to manage patients during follow-up

- Implement very frequent monitoring visits after patients enter follow-up; if at any time they meet the criteria for ALT flares, then frequency needs to increase to weekly visits until the flare is dealt with
- If there are any signs of decreasing liver function during follow-up, the patient needs to be immediately re-initiated on NUC treatment
- Three different situations: if they are present, ask investigators to confirm
 - HBV DNA > 2000 IU/mL and ALT > 5xULN
 - HBV DNA > 20,000 IU/mL
 - Confirmed HBeAg seroreversion
 - Don't do confirmation immediately after these initial results; do them four weeks apart
 - If results are confirmed, consider NUC retreatment

Presenter: Luisa Stamm, *Assembly Biosciences*

Title: Lessons Learned from Phase 2 Studies 201 and 211

Slides: <https://bit.ly/3luIvHS>

Study 201: Addition of VBR to NrtI Results in Deeper Viral Suppression

- 24-week placebo-controlled study in which virologically suppressed, HbeAg(-) or HbeAg(+) patients with no or minimal fibrosis received placebo or vebicorvir on top of their NrtI, for 24 weeks.
- The addition of VBR to NrtI led to deeper viral suppression

Study 211: Stopping Criteria to Assess for Off-Treatment Virologic Response

- Eligible patients then rolled over from study 201 to study 211, the open-label extension in which all patients received VBR + NrtI
- Following a year or a year and a half of deep viral suppression with both core inhibitor and NrtI, there was an assessment of stopping criteria, shown in the purple box on the right of the slide, which was determined through feedback from investigators and discussion with the FDA, for protocol amendment
 - A patient had to have had HBV total nucleic acids < 20 IU/mL and be either HBeAg(-) or with a low HBeAg of less than or equal to 5 IU/mL and have both of these for at least 6 months at the time of assessment
- in total 23 HBeAg(-) and 18 HBeAg(+) patients discontinued treatment in the study and were monitored monthly for safety and virologic response

Study 211: Off-Treatment HBV DNA Graphs

- All patients relapsed, and 2/3 restarted NrtI during the study per protocol criteria
- A post hoc analysis in each group identified two categories of patients, with off-treatment viral loads which were lower (green) or higher (purple) with a cut-off of 80,000 IU/mL.

This allowed them to do a univariate analysis for factors associated with off-treatment response. Entecavir use and lower correlated antigen levels at the end of treatment were identified as being associated with lower viral loads in the HBeAg(-) group, and with younger patients with a cutoff of 45 years in the HBeAg(+) patients

Summary and Lessons Learned from Studies 201 and 211

- More potent core inhibitors and other agents with complementary mechanisms of action are likely required for finite and curative treatment regimens for chronic Hepatitis B
- For the future, stopping criteria will need to be refined and based upon the post-hoc analysis, may include additional antigen components, perhaps depending on the different mechanisms of action of the investigational regimens
- Importantly, discontinuation of VBR + NrtI in the study was well tolerated by the patients, with limited AEs and ALT elevations which occurred just post-NrtI restart in the setting of high viral loads. There were no events of hepatic decompensation.
- Based on this, stop NUC studies may be conducted in a way that is safe for patients with no or minimal fibrosis and with continued close monitoring

Presenter: Anna Maria Geretti, *Roche*

Title: Stopping NUC Therapy in Piranga

Slides: <https://bit.ly/3zgvQNY>

The Piranga Phase 2 Study

- Recruiting virologically suppressed patients on NUC therapy for at least 12 months
- Primary endpoint for efficacy: percentage of patients with HBsAg loss at 24 weeks post-end of treatment
- This is a platform study that started in July 2020

Piranga Schematic

- Concept: to study multiple targeted finite therapies in an ongoing manner, with therapies allowed to enter or leave the platform on the basis of a decision algorithm
- Slide intended to highlight how different combinations, that include some combinations with immunomodulators and others without, come onto the platform at different times
- There is a NUC control arm that doesn't receive any new molecular entity (NME) and works as a control

Piranga: Criteria for Stopping NUCs

- Participants will stop NUCs at any time during the follow-up period if samples taken at end of treatment (week 48) or at any of the follow-up visits show:
 - 1. ALT <1.25 x baseline values, *AND*
 - 2. HBV DNA <LLOQ or <20 IU/mL, *AND*

- 3. Negative HBeAg (if HBeAg positive at baseline), *AND*
- 4. HBsAg at EoT <100 IU/mL (or >1 log reduction from baseline, under review)
- There is also wording in the protocol referring to an alternate criterion where the HBsAg can be higher than 100 IU/mL, but there is more than one log reduction from baseline. But this particular aspect is currently under review
- Some comments received (dated to 2019)
 - From FDA: Benchmarks that must be met for NUC discontinuation in combo arms: at a minimum, ALT <1.25 X ULN, HBV DNA <LLOQ, HBeAg negative. Also open to consider an absolute threshold in HBsAg level at EoT (in addition to a treatment-induced decrease)*
 - *noting that HBsAg decline to a certain plateau is currently not
 - LLOQ = lower limit of quantification
 - From EMA's – Same approach advised for discontinuation in NUC control arm as per other arms

Piranga: Secondary efficacy endpoints

- Measuring the kinetics of HBsAg, as well as measuring the HBcrAg and Hepatitis B RNA
- See slide for other endpoints

Presenter: Susanna Tan, *Gilead Science, Inc.*

Title: Gilead: Stopping NUCs in HBV Cure Trials

Slides: <https://bit.ly/3EyXPMz>

- Ongoing phase-2 HBV cure trials
- Goal: finite therapy leading to functional cure, defined as durable loss of serum HBsAg
- Doing this in a combination fashion, with immune modulators as well as antivirals
- In virally suppressed patients who are on NUCs at some point, to achieve this finite therapy regimen, we do need to stop NUCs at some point
- In the current trials, their approach has been to test a lot of combination regimens of various duration
 - At the end of treatment, subjects will be evaluated for whether:
 - HBV DNA <20 IU/mL
 - HBeAg negative
 - HBsAg less than or equal to 100 IU/mL
 - If they meet these criteria, they recommend stopping NUCs at that point, and then patients would be off their NUC, and they would be assessing for achievement of functional cure at their primary endpoint
 - Their primary endpoint is the proportion of subjects who achieve functional cure, defined as HBsAg loss as well as HBV DNA <20 IU/mL

- Compare this across different combination regimens for optimal outcomes from the primary endpoint status

Presenter: Poonam Mishra, *FDA*

Title: Trial Designs (Flares and Mitigating Risk): FDA Perspective

Slides: <https://bit.ly/3hBaBQM>

Trial Design

- Randomized controlled trials are recommended in order to allow for direct comparison
- Trials may demonstrate superiority or non-inferiority
- Appropriate trial design depends on the patient population being studied and the treatment regimen being evaluated
 - Investigational drug vs. Placebo – feasible in population with inactive disease in whom treatment is not recommended (*per current treatment guidelines*)
 - Investigational drug vs. NrtI or IFN alone (active control) – in patients with active disease
 - Add-on to current therapy – in patients virally suppressed on NrtIs (Investigational drug + current Rx vs. Placebo + current Rx)

Benefit-Risk Assessment in Drug Regulatory Decision Making

- This is a systematic process
- To be approved for marketing, a drug must be safe and effective for its intended use
- Effectiveness requirement: substantial evidence that the drug will have the effect it purports or is represented to have under proposed labeled conditions of use
- “Safe” for use: Interpreted as the determination that a **drug’s benefits outweigh its risks** to the intended population
- Benefit-risk assessment: benefits outweigh potential risks to the intended population

FDA’s Benefit-Risk Framework

- Informed by the review of the evidence of the drug’s safety and efficacy as submitted by an applicant
- Also informed by many other factors, as shown in the framework on this slide
 - Analysis of condition
 - Current treatment options
 - Benefit
 - Risk and risk management

Safety Monitoring in Phase 2/3 Trials: Key Considerations

- See slide for key considerations
- Specific safety monitoring may be needed, and plans should be in place

- Changes in safety monitoring plans may be warranted based on data from the trial

Hepatic Flares

- Three different broad categories of flares have been proposed
- Close monitoring of ALT elevations is necessary
- Prespecified criteria for monitoring flares should be in place

Liver Safety Evaluation: HBV Forum Initiative

- Prespecified algorithmic approach to the evaluation and management of liver safety signals
 - Interpretation of ALT flares in context of other biomarkers
 - Evaluation of liver safety signals during various stages of the study
- Crucial that systematic data collection is done, and full diagnostic workups should be done to rule out alternative causes of liver injury

HBV Treatment Discontinuation

- Development of new therapies is targeted at finite treatment regimens
- Criteria for stopping therapy should be well-defined in the protocol
- Long duration of follow-up is needed for patients who remain off-therapy

Stopping NrtI Therapy

- Needs to be systematically assessed
- Severe acute exacerbations of HBV infection may occur after discontinuation of anti-HBV therapy, particularly in the absence of HBsAg loss

Patient's Voice in Drug Development

- Need more understanding of patient experiences, preferences and input
- Need to talk directly with those affected

Resources and Conclusions

- See slides for list of resources
- Benefit-risk assessment is the foundation for the FDA's regulatory review of human drugs and biologics
- Multidisciplinary assessment of safety risks continues throughout the drug's lifecycle
- Avoiding unreasonable and significant risk to clinical trial participants and patients is paramount
- Collaborative discussions between academia, industry, regulatory agencies, and patient advocacy groups are crucial for efficient drug development

- FDA remains committed to facilitate the development of safe and effective therapies for people living with chronic HBV infection globally
-

Presenter: Stephanie Buchholz, *BfArM*

Title: Stopping NUCs – Flares and mitigating risk: Regulatory considerations for clinical trial design for novel combination therapies with a finite treatment duration in CHB patients who are virologically suppressed on NUCs

Slides: <https://bit.ly/3tJvQ7E>

Types of HBV cure covered by approved drugs

- NUCs and interferons are only partial cures and are all we have
 - All other types of cures are goals of future therapies
- Complete and sterilizing cures are currently not considered achievable, based on the tools we have currently

Trial Design Considerations – Finite therapy in CHB patients who are virologically suppressed on NUCs

- Required for European trials: Well controlled randomized trials in the proposed population with an approved active control arm
- Clinical trial with two arms: Investigational product (s) + NUC vs. NUC alone
- Study population: CHB patients virologically suppressed on NUCs (most likely HBeAg pos/neg patients)
- Primary efficacy endpoint: Sustained suppression of HBV DNA (< LLOQ) with HBsAg loss (< 0.05 IU/ml) with or without anti-HBs after treatment discontinuation
- Treatment duration: Finite treatment duration dependent on the Mechanism of Action and half-life of the drug

Criteria for Stopping NUCs EOT

- Increasing evidence that stopping long-term NUC therapy results in HBsAg-loss rates of up to 20%
- Criteria of stopping NUCs in clinical trials should be
 - Applied equally across treatment arms
 - Well-defined in the protocol
 - Stringent (e.g. HBsAg loss or marked reduction of other biomarkers identified)
- Remaining question: Do baseline demographic or disease characteristics, i.e. HBeAg status or prior duration of suppression with NUC impact the importance of discontinuing NUCs in terms of efficacy and safety?

Criteria for stopping NUCs EOT – variables to consider

- Potential impact of baseline demographic and disease characteristics on response rates after stopping NUCs → effect on efficacy outcome

Catalyzing Clinical Research to Improve Global Health

1608 Rhode Island Avenue NW • Suite 212 • Washington DC 20036 • www.forumresearch.org

- Reflected in the study design (inclusion/exclusion criteria, stratification criteria and pre-defined subgroup analyses)
- See slide for variables to consider for the study design to ensure comparability between IP arm and control arm
- Potential labelling consequences!!! (At the time of marketing authorization)

Safety considerations – hepatitis flares

- Stopping NUC treatment is often associated with hepatitis flares
- HBsAg loss is not necessarily associated with severe flares
- Highlights the importance of assessment of on and off-treatment hepatitis flares in clinical trials in order to differentiate between potentially beneficial immune clearance flares and severe flares
- Severe flares associated with increase in bilirubin or prothrombin time can be serious and life-threatening
- Detailed safety monitoring plan for evaluation of hepatitis flares should be included in the clinical study protocol (low bar for monitoring flares recommended, i.e. 2x ULN)
 - In order to best catch all flares and differentiate between beneficial and severe flares
- Definition of unambiguous predefined treatment discontinuation and trial stopping rules
- Treatment re-initiation criteria for NUC should be predefined in the protocol

Safety considerations – Risk factors for detrimental withdrawal flares

- See list on slide
- Impact on the study design should be considered (inclusion/exclusion criteria, safety monitoring plan, stopping rules, re-treatment criteria)
- This will ensure the safety of the study population

Trial Design – Safety Considerations

- Benefits should outweigh the potential risks for the intended population
- Avoidance of unreasonable and significant risks for clinical trial participants
- All serious hepatic events (deaths, liver transplantation, hepatic decompensation, cases of severe hepatitis flares) and immune system related events (autoimmunity/extreme immune response) should be systematically evaluated
- Independent safety data reviewing committee is recommended

Timing and Response Rates

- Timing of assessment
 - Off-treatment response for Phase IIb/III trials
 - May depend on mechanism of action and half-life of the drug
- Response rates

- Must be sufficiently high to outweigh the risk for DILI/flare related morbidity and substantial remaining uncertainties in order to support approval
- Benefit/Risk Considerations for regulatory decision making
 - Benefit: magnitude and durability of response
 - Risk: safety profile, risk potential
 - Relation to approved therapeutic options (benefit-risk)

Trial Design – Follow-Up and Long-Term Follow-Up

- Adequate long-term follow-up data will be required to support approval
- Adequate FU to monitor for durability of response and observational clinical data on clinical events (timing is dependent on mechanism of action and treatment duration)
- Post-treatment relapses and resistance development should be evaluated
- Appropriate long-term follow-up should be planned and defined at time of application to assess durability of sustained response and long-term clinical outcome
- Evaluation of incidence of liver-related complications (hepatic failure, HCC, liver transplant and liver-related deaths)
- Documentation of late post-treatment relapses

Conclusions

- Stopping NUCs at EOT in clinical trials aiming at functional cure in CHB patients who are virologically suppressed on NUCs with a finite treatment duration, requires careful considerations on the clinical trial design, due to the potential impact of baseline demographic and disease characteristics on response rates after stopping NUCs (efficacy) and the occurrence of hepatitis flares (safety)
 - Slide includes additional notes on efficacy and safety

Presenter: Kosh Agarwal, *King's College London*

Title: Stopping NUCs: how to move forward? (With incomplete knowledge...)

Slides: <https://bit.ly/3ziN9NU>

Stopping NA therapy before HBsAg loss in HBeAg-negative patients

- Slide showing all of the different potential outcome predictors, which may or may not be relevant in a world of new types of drug mechanisms

Viral and immune factors associated with successful withdrawal in HBeAg -ve HBV (Garcia-Lopez et al J Hep 2020)

- 27 patients undergoing withdrawal
- Low SA_g
- Decreased cccDNA transcription
- Function HBV specific T cells at baseline

Conclusions

- No clinical consensus
 - Not a big uptake in clinical practice – patients are not finding this an attractive paradigm in clinical practice
 - What endpoint? – surely SAg (surface antigen) loss
 - Low SAg <100 – lower the better
 - Conflicting evidence regarding newer viral biomarkers
 - Viral/host heterogeneity is confusing
 - Transcriptional activity vs. invigorated T cell response
 - Pragmatic criteria (HBV EA_g loss, HBSAg <100, composite)
 - Standardize – i.e. everyone and then watch? ... or consider MOA driven rules
-

Presenter: Marion Peters, *Northwestern University*

Title: When to Re-Treat after Stopping NrtI

Slides: <https://bit.ly/3nK9fHj>

When to restart NrtIs

- Don't stop NrtIs in those with cirrhosis
- All patients who stop NrtIs should be monitored closely: ALT, HBV DNA and clinical assessment q1-3 for 3mos, q3 mos for 1y at least
- Clinical decompensation or increased bilirubin, INR: an indication to restart NrtI
- What about elevated ALT and HBV DNA?
- What about in studies of new drugs: DAAs or immunomodulators?

When to re-start NrtI: EMA FDA

- Stringent treatment re-initiation criteria for restarting NUCs should be predefined in the protocol
- Time of assessment requires
 - Long term f/u of off-treatment responses for Phase IIb/III trials
 - May depend on mechanism of action and half-life of the drug

When to re-start NrtI

- Agreement
 - Liver decompensation
 - Treating MD
 - Patient request
- Similarities but not true agreements
 - Very high ALT >10x ULN
 - Moderate ALT with HBV DNA

- HBeAg seroreversion
- Close monitoring
- Any evidence of liver dysfunction- immediately- everyone agrees with
 - Elevated bilirubin
 - Elevated INR
 - Development of ascites, encephalopathy
- HBeAg sero-reversion
- All protocols agree on “Treating physician” or patient preference
 - Assembly Bio half restarted NUCs for this reason (EASL 2021)
 - And not for the pre-defined specific requirement for restarting NUCs
- Level of HBV DNA and ALT vary

Markers to predict need to restart

- Those with HBV Control
 - Reactive HBV specific CD8 higher in those who decreased qHBsAg (PO-430 Asensio)
 - HLA diversity higher in those who did not relapse (Tuefferd PO947)
- Relapsers
 - Anti-HBc higher (cut off <325 IU/mL: Cornberg PO-2293)
 - Higher HBcrAg (Sarowar Toronto Stop PO-2269)

Can we predict who will need retreatment?

- Slide from Van Bommel et al
- Multiple small studies showing undetectable HBcrAg and/or low qHBsAg at the time of stopping = lower risk of relapse & increased chance of HBsAg loss
- Need more data but could be promising predictive tools

Slide from EASL 2021 (Sarowar)

- Those who were retreated had higher correlated antigen than those who did not need retreatment
- This is for stopping NUCs, but HBV RNA did not differ

Slide from study of 3 RCTs of Peg IFN

- Looked at the rate of sustained response 6 months after treatment withdrawal
- Differed from the study showing correlated antigen was important
 - Yes, it is important, and those who had high correlated antigen had the lowest rate of sustained response. But if you look to the left, those who had low HBV RNA had good, sustained response and those who had high or detectable HBV RNA had very low sustained response. On the right, if you look at both low surface antigen and low detectable HBV RNA, they’re the ones with the best response and where they were high, they did not have a response, suggesting that it may be different markers for NUCs or DAAs versus immunomodulators

Issues for evaluating when to restart in trials

- Safety first
- **Stringent** treatment re-initiation criteria for NUC should be predefined in the protocol
 - How to deal with MD/patient preference?
- Monitoring criteria

Issues for evaluating when to restart in trials

- Monitoring criteria
 - Liver decompensation all agreed to restart
 - How frequent to monitor?
 - Some do every week if ALT levels abnormal
 - For stopping NUCs we usually monitor every month
 - Should we change that in DAA studies?
 - For how long?
 - Should criteria differ by type of therapy studied?
 - E.g. siRNA (longer half life) vs CAM vs IM
 - Is it possible to standardize monitoring within MOAs?
 - MOA = mechanisms of action
 - Will this help with new studies of DAAs and immune modulators?
 - Is it possible to standardize monitoring across MOAs?
 - This will be a lot harder
- What to monitor?
 - ALT, HBV DNA, clinical assessment – sufficient to restart NrtI?
 - HBcrAg, HBV RNA, qHBsAg, HBV sp CD8 – earlier to predict need to restart?

Audience Q & A

Moderators:

- Harry Janssen, *University of Toronto*
- Nezam Afdhal, *Beth Israel Deaconess Medical Center*

We talked about stopping NUCs as if there was one type of NUC. Should we actually be thinking about which NUC we are using in terms of trial design and from the perspective of the regulators?

- AssemblyBio: For treatment naïve studies, entecavir is provided as part of the clinical trial. In the NUC suppressed studies, the patients can come in with any NUC that they're taking

- Different responses were seen in the patients depending on the NUC, with those on entecavir (ETV) having later relapse and lower off-treatment viral loads compared to tenofovir-based treatment
- Not a clear answer on why, but it is an important question to think about
- Other Responses
 - People with tenofovir seem to relapse quicker over time, versus entecavir has slower DNA relapse
 - Need to follow people longer; but compliance and follow-up may be difficult
- Regulatory perspective
 - New data is becoming available
 - Talk with different companies about the influence of different NUCs, especially when you are investigating combination therapies
 - Pre-defined sub-group analysis prior to the start of the study should be made in order to identify potential differences
 - More data is needed to make it more reliable

We are talking about stopping NUCs in clinical trials, not in terms of clinical practice. Essentially in trials this means stopping everything. There's a huge variation in the design of trials and a huge issue in terms of mechanism of action and what markers you're looking at. From the perspective of duration, is there a minimum and/or maximum duration of therapy you are considering in these newer studies? Or is there a plan to use biomarkers to guide the therapy? What is the current thinking from our industry colleagues?

- We are thinking of treatments with finite duration and in order to be considered finite, it cannot be that long because otherwise you are talking about chronic treatments
 - Maximum duration has been 48 weeks
- A challenge to this response: if current NUC care is lifelong in HBeAg(+) patients, finite does not have to be 48 weeks, it can be 96 weeks, etc. because it is still finite. So, what other considerations go into the duration?
 - Safety; pharmacoeconomic considerations; etc.
 - If something doesn't work after the maximum duration, does that mean that the drug didn't work?
 - Response: Another consideration is the complexity of the treatment and how long can you ask patients today to participate in such long studies. Is this actually helping the field?

Is it only the level of HBsAg or also the speed at which the HBsAg level goes down to say whether we will eventually reach functional cure and not need to restart NUCs?

- This is the key question, because we are talking about new drugs with new mechanisms of action
- We can't extrapolate from NUCs alone or interferon; we need to see the data from other things and use it to predict how we are going to stop

To what extent can we use the new biomarkers to predict whether patients can be stopped on NUCs? The sensitivity of the assays may be low.

- We are going to need to understand these markers as surrogate markers and really understand them when we are selecting patients for stopping NUCs
- Need to address things systematically in early phases of trials so we have better data to rely on

We have a lot of different treatment modalities. We are dealing with a lot of different MOAs. To what extent does that really determine when we would start treatment? Some have different half-lives, modifying agents, etc.

- Something companies are thinking about for their next trials. Struggle with what to do with HBsAg because some comes from integrated forms.
- We are in the world of finite therapy, but the MOA and combinations really need careful thought.
- Restarting is about safety, and we heard that very clearly. But the different MOAs for predictors and duration are going to be different and relevant

Follow-Up Question: Should there be immunological markers included in addition to biology markers when doing combinations and if so, which one?

- Yes, but not sure which
- Some data suggesting HBV-specific CD8's
- The question is ease of markers; everything should be studied in a trial situation and whether that gets translated to a clinical situation depends on the ease of the markers and evaluating them
- Need to think about underlying combination regimen that is being used

Are industry colleagues concerned about the heterogeneity of the patients that are included in trials? Should we be recruiting and stratifying patients for these core studies in a more stringent way?

- They are trying to run homogenous studies, but this can be difficult, so they try to strategize the patients the best they can
- In the ideal situation you cure a heterogenous group, but really in the beginning you look at where you can actually achieve functional cure groups and in which subgroups and go from there

If we look at the patients with a really low HBsAg level, what will the HBsAg loss rate be in these patients, and how will this differ among Asian/Caucasian patients?

- Mostly race seemed to be very predictive
 - Could have been that more Asian patients were HBeAg(-) at start of therapy and therefore had lower rates of HBsAg loss