Stopping Finite Treatment Working Group Update

HBV Forum 8

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London, UK

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THE FORUM For Collaborative Research℠

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Background

- Functional cure:
  - Negative HBsAg, normal ALT +/- anti-HBsAb off-treatment
    - Requires stopping treatment to test
- Data on stopping NrTI: mixed
- Dearth of data on stopping all treatments with new agents
  - Different MOAs of new drugs
    - Assessment of functional cure during and/or after treatment
  - Role of cccDNA and iDNA for HBsAg

Importance

- Finite treatment requires treatment discontinuation
- Consensus needed among clinical researchers, patients, pharmaceutical/diagnostic companies and regulatory agencies to inform clinical research programs
- Safety *and* Efficacy

Working Group Objective

- Review and identify areas of consensus among stakeholders
- Identify gaps and recommend steps to fill these gaps

- Recognizing “dearth of data” on treatment discontinuation
  - Base discussions on science wrt MOA, virology, existing clinical data
  - Evolve recommendations as more data and diagnostic tools become available

Working Group Members

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Kosh Agarwal (co-lead)	Harry Janssen	**Marion Peters (co-lead)**
Thomas Berg	Pietro Lampertico	Luisa Stamm
Stephanie Buchholz	Isabel Lonjon-Domanec	Norah Terrault
John Fry	Mala Maini	Su Wang
Ed Gane	Patricia Mendez	MF Yuen
Anna-Maria Geretti	Veronica Miller	
Carey Hwang	Poonam Mishra	

Question 1 (TB, MP, AMG)

- Goal of SFT is functional cure.
  - What about loss of replication from cccDNA when subject is still HBsAg positive from iDNA?
  - Should HBsAg loss from serum be essential for sustained off-treatment remission (i.e., HBV DNA <LLOD, ALT <ULN) if HBsAg is from iDNA?
  - Can we differentiate between cccDNA and iDNA derived sAg?

Question 2 (EG, JF, LS)

- How do data from stop NrtI inform framework for stopping:
  - replication inhibitors (RIs i.e. CAMs, NUCs)
  - translation inhibitors (TIs i.e. siRNAs, ASOs)
  - HBsAg secretion inhibitors and immunomodulators (IMs)?
- Should we discuss other MOAs not yet being studied?
- What about combinations of multiple mechanisms of action (MOAs)?

Question 3 (PL, NT, PM)

- 1) Should different demographics (age, gender, phases, genotype, fibrosis stage, treatment experiences vs naïve etc) have difference framework for SFT? (efficacy only)
- 2) How to identify NrtI treated patients with advanced fibrosis to exclude from studies? (safety)

Question 4 (MFY, EG, CH, PL)

- What level of qHBsAg should be attained before SFT?
  - Will this differ between different modes of actions?
- Is anti-HBsAg important?
- How long should therapy be continued after reaching stopping criteria (HBsAg <LLOD or <10)?
- Can on treatment responses inform this?

Question 5 (NT, KA)

- Should there be intensive therapy followed by suppressive therapy? (NrTI +/- CAM)
- Should NrTI be continued after stopping other finite treatments?
  - Can treatment responses inform this?
- Efficacy endpoint: will continuing NrTI monotherapy post-novel therapies improve or reduce sustained HBsAg loss?
- Safety endpoint: will continuing NrTI monotherapy post-novel therapies reduce risk of severe flares, decompensation, death?

Question 6 (KA, ILD)

- What is the framework for restarting suppressive therapy/Nrtl.
- Will the restart framework differ for different MOAs?

Question 7 (MFY, TB)

- Are there virologic biomarkers that can/should be studied to inform SFT at baseline or EOT?
  - Blood/FNA/Biopsy?

Question 8 (MM, MP)

- Are there immune markers that can/should be studied to inform SFT at baseline or EOT?
  - Serum/ PBMC/ FNA/ Biopsy

Next steps

- Project initiated December 2021
- Finalize first draft – June 30th
- Revise for final submission
- Submit by end of July 2022

Special thanks > WG Coordination

- Emily Gainor
- Chelsey Campillo
- Mitchell Leus

Thank You!