Achieving functional control of HBV and HDV infection with nucleic acid polymer-based combination therapy

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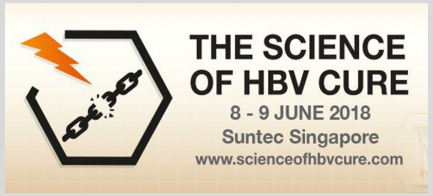

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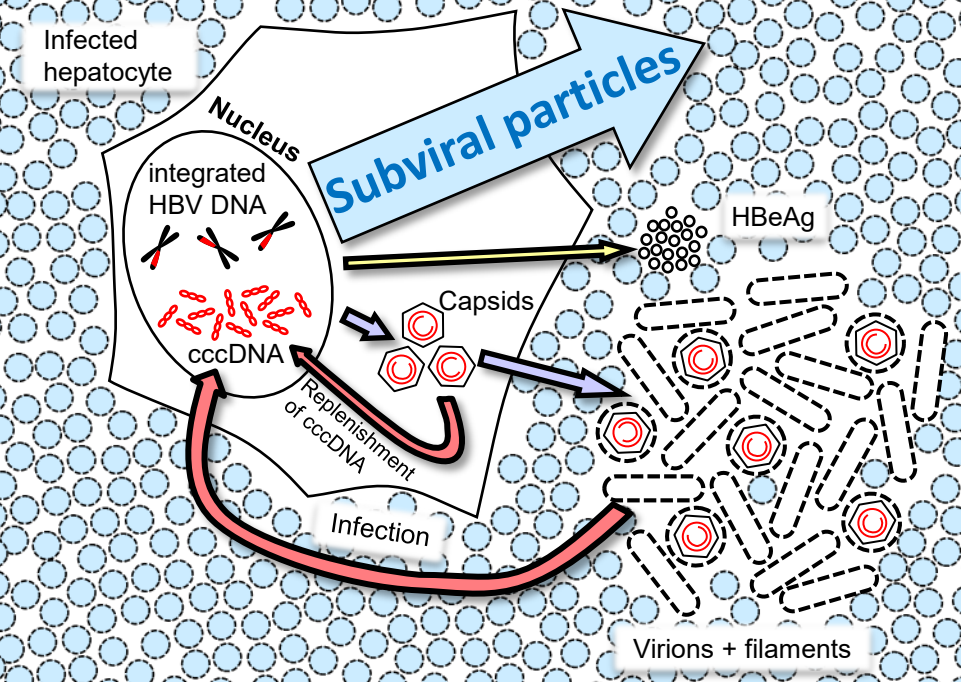
Particle production in HBV

THE HBsAg PROBLEM:

almost all HBsAg is derived from subviral particles

(and most likely from integrated HBV DNA)



HBsAg is an immunosupressor:

- Masks anti-HBs response
- Blocks signalling mechanisms in innate and adaptive immunity
- Blocks the effect of immunotherapies
- **HBsAg clearance is crucial to achieving functional control and remission of HBV infection**

Aillot et al., Antimicro. Agents Chemother. 2018; 62: e01741-17
Rydell et al., Virol. 2017; 509: 67-70
Bazinet et al., 2017 Lancet Gastro. Hep 2: 877-889
Al-Mahtab et al., 2016 PLOS One 11: e0156667
Yang et al., Int. Immunopharmacol. 2016; 38: 291-297
Jiang et al., J. Viral Hep. 2014; 21: 860-872
Wang et al., J. Immunol. 2013; 190: 5142-5151
Kondo et al., ISRN Gastro. 2013; 2013:935295

How important is HBsAg loss during finite therapy?

Removal of NUC therapy is only indicated with sustained HBsAg loss / seroconversion

2017 EASL / 2018 AASLD treatment guidelines
Kho-Herman and Chen, Liver Res. 2017 1: 135-139.

Viral rebound following removal of NUC therapy is infrequent when HBsAg is < 100 or 200 IU/mL

Liang et al., Aliment. Pharmacol. Ther. 2011; 34: 344-352
Chen et al., J. Hepatol. 2014; 61: 515-522

TDF or ETV alone can achieve clearance of intrahepatic cccDNA (HBcrAg < LLOQ, liver biopsy negative)

but removal of these NUCs leads to immediate rebound in all patients when HBsAg is still present!

Lai et al., Hepatology 2017; 66: 512A

Sustained (24 week) HBsAg loss following 48 weeks pegIFN/TDF is predicted by extent of HBsAg reduction during therapy

HBsAg decline > 3.5 $\log_{10}$ IU/mL: 80% PPV, 99% NPV

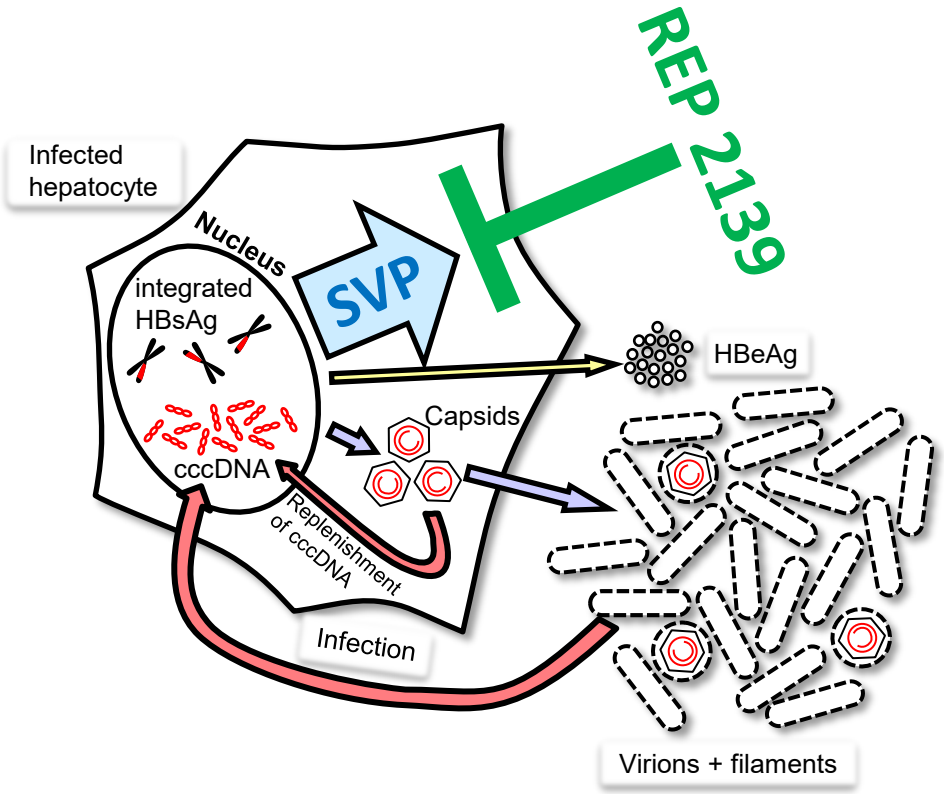
Marcellin et al., Aliment. Pharmacol. Ther. 2016; 44: 957-966

REP 2139 mechanism of action in HBV

REP 2139 blocks subviral particle release
from cccDNA and integrated HBV DNA

→

Efficient HBsAg clearance
from the blood



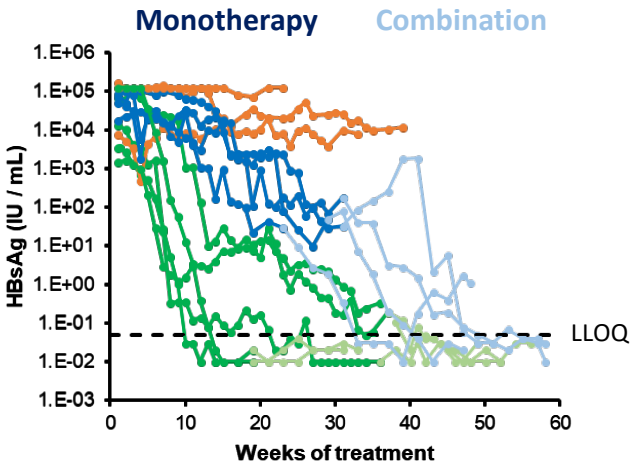
REP 2139 prevents HBsAg replenishment only.

HBsAg clearance is dependent on the clearance of SVP by host immune function.

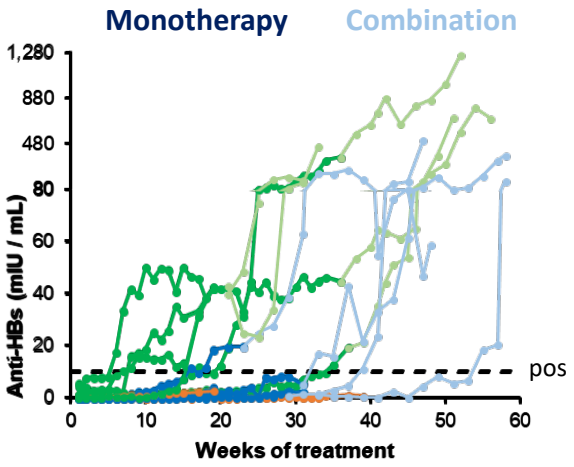
Building a combination regimen with HBsAg loss

Step 1: is the antiviral effect of immunotherapy improved with HBsAg reduction / loss?

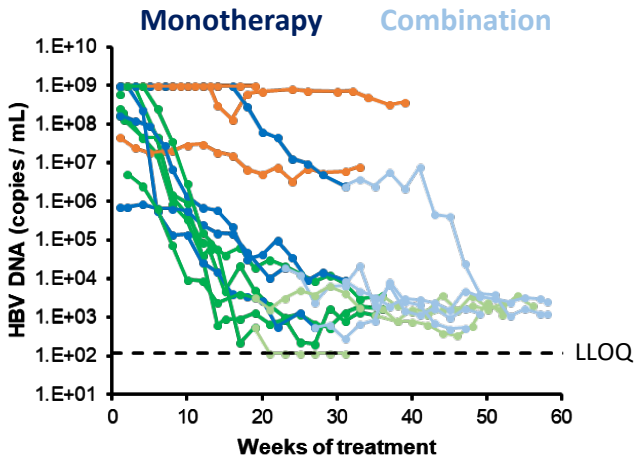
REP 102 study - HBeAg positive chronic HBV infection
9 patients with > 2 log HBsAg reduction on REP 2139-Ca monotherapy transitioned to combination therapy: 13-26 weeks of thymosin alpha 1 (n=4) or pegylated interferon alpha 2a (n=5)



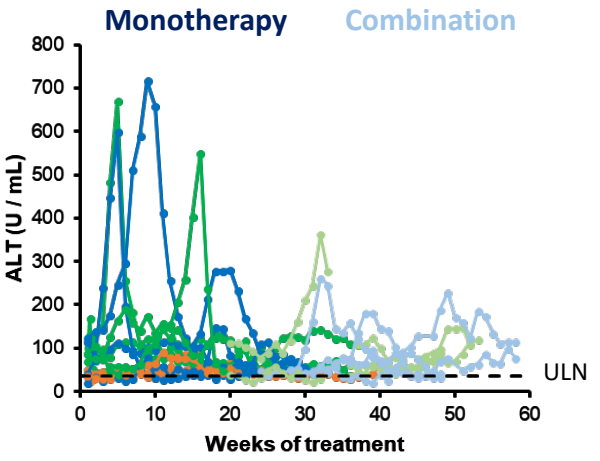
HBsAg decline continues / accelerates



Anti-HBs dramatically increased



HBV DNA decline brought to a low threshold in all patients



Additional but weaker flares observed during immunotherapy **(all otherwise asymptomatic)**

< 1 log reduction in HBsAg | HBsAg > 1 log reduction but < 1 IU/mL | HBsAg < 1 IU/mL

Al-Mahtab et al., 2016 PLoS One 11: e0156667

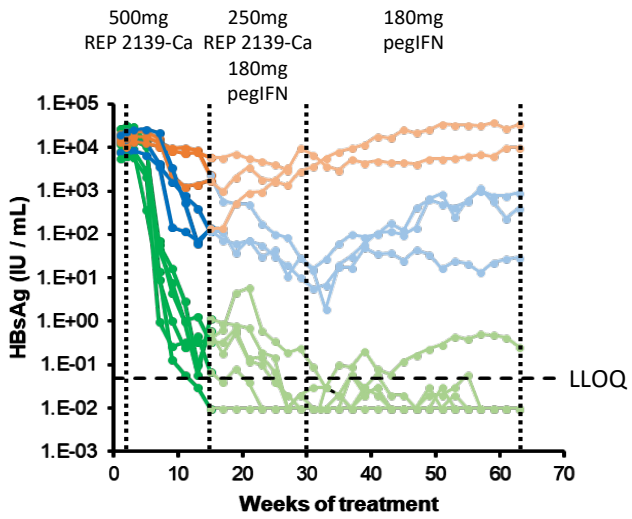
Building on functional control rates…

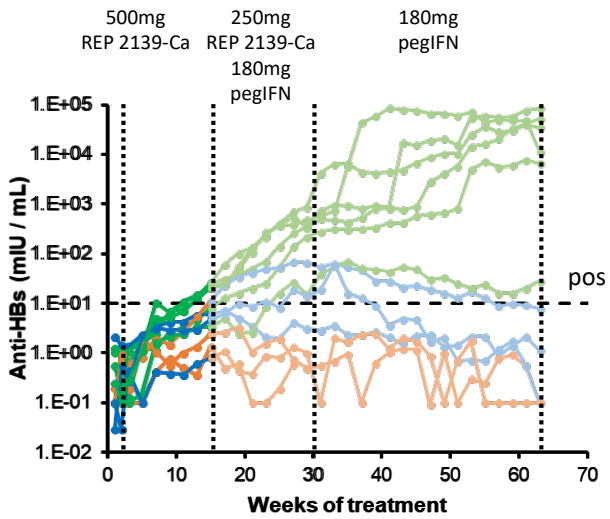
Mode	Monotherapy	Combination therapy		
Study	REP 101	REP 102		
NAP	REP 2055	REP 2139-Ca		
Immunotherapy	none	pegIFN **thymosin alpha 1**		
NUC	none	none		
Population	HBeAg positive HBV mono-infection	HBeAg positive HBV mono-infection		
Number treated	8	12 (9 received combination)		
Follow-up: Functional control HBV DNA < 1000 IU/mL		8/9 initially 4 @ 2 years (HBsAg < 1 IU/mL)		
Follow-up: Functional control HBV DNA < LLOQ	3 @ 1 year 2 @ 5 years (HBsAg = 0.08 and 0.03 IU/mL)			

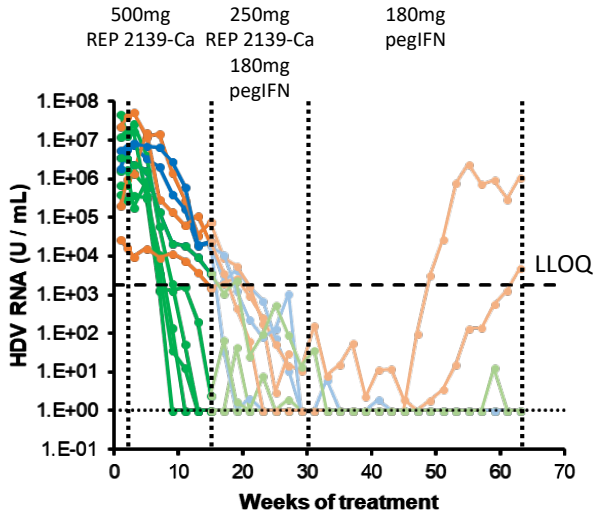
Building a combination regimen with HBsAg loss

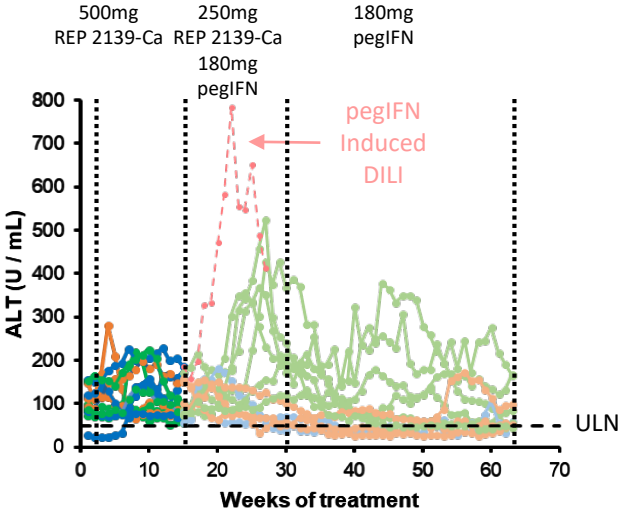
Combination effect in HBeAg negative HBV / HDV co-infection?

REP 301 study - HBeAg negative chronic HBV / HDV co-infection
12 patients on REP 2139-Ca monotherapy transitioned to combination therapy with pegIFN followed by consolidation with pegIFN monotherapy









HBsAg decline continues / accelerates
(but not in non-responders)
(slow rebound after removal of REP 2139)

Anti-HBs dramatically increased
(only in patients where HBsAg < 1 IU/mL before pegIFN)

HBV RNA TND in 11/12 patients during therapy
(rebound in non-responders after removal of REP 2139)

ALT flares observed during immunotherapy
(all otherwise asymptomatic)
(only in patients where HBsAg < 1 IU/mL before pegIFN)

< 1 log reduction in HBsAg | HBsAg > 1 log reduction but < 1 IU/mL | HBsAg < 1 IU/mL

Bazinet et al., Lancet Gastro. Hepatol. 2018; 2: 877-889

Building on functional control rates…

Mode	Monotherapy	Combination therapy		
Study	REP 101	REP 102	REP 301	
NAP	REP 2055	REP 2139-Ca	REP 2139-Ca	
Immunotherapy	none	pegIFN **thymosin alpha 1**	pegIFN	
NUC	none	none	none	
Population	HBeAg positive HBV mono-infection	HBeAg positive HBV mono-infection	HBeAg negative HBV / HDV co-infection	
Number treated	8	12 (9 received combination)	12	
Follow-up: Functional control HBV DNA < 1000 IU/mL		8/9 initially 4 @ 2 years (HBsAg < 1 IU/mL)		
Follow-up: Functional control HBV DNA < LLOQ	3 @ 1 year 2 @ 5 years (HBsAg = 0.08 and 0.03 IU/mL)		6 HBV DNA < LLOQ @ 2 years 7 HDV RNA TND @ 2 years (4/12 HBsAg ≤ 0.05 IU/mL)	

Adding a another direct acting antiviral

Which one to choose?

Adenosine based NUCs (ADV and TDF) efficiently inhibit the HBV RT

but all are also bifunctional agents with immunotherapeutic properties

- bind to the purine P1 receptor
- activate the production of various cytokines including TNFα and INFγ
- stimulate the production of INFλ3 in patients

also have a direct effect on reducing cccDNA levels in the liver

Improved liver partitioning of tenofovir pro-drugs may increase the immunotherapeutic effects of tenofovir in the liver:

TXL >> TAF > TDF

These immunotherapeutic effects may become significant with reduction of HBsAg

Zidek et al., Nucleosides Nucleotides. 1999; 18: 959-961
Zidek et al., Antimicrob. Agents Chemother. 2001; 45: 3381-3386
Zidek et al., Eur. J. Pharmacol. 2003; 475: 149-159
Kmoníčková et al., Eur. J. Pharmacol. 2006; 530: 179-187
Potměšil et al., Eur. J. Pharmacol. 2006; 540: 191-199
Zidek et al., Eur. J. Pharmacol. 2007; 574: 77-84
Kostecká et al., Int. Immunopharmacol. 2012; 12: 342-349

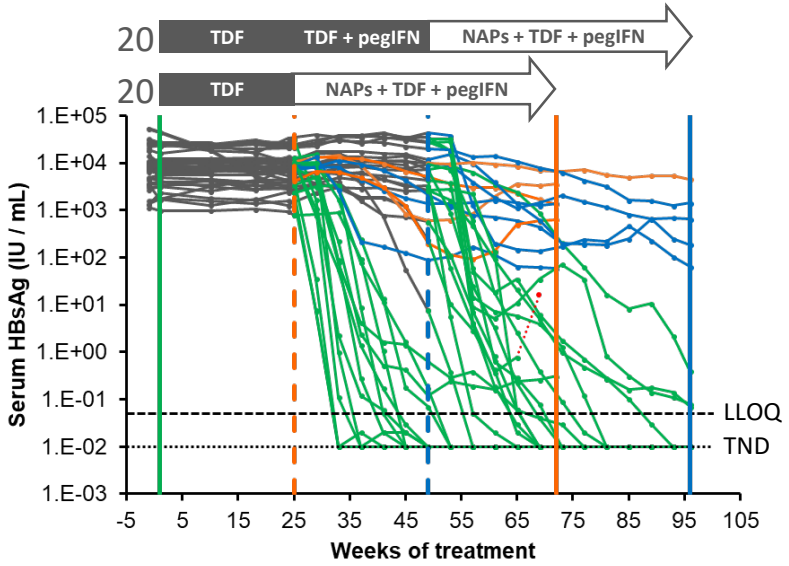
Murata et al., Gut. 2018; 76: 362-371

Cathcart et al., J. Hepatol. 2018;66: S476
Lai et al., J. Hepatol. 2017; 66: 275-281
Werle-Lapostolle et al., Gastroenterol. 2004; 126: 1750-1758

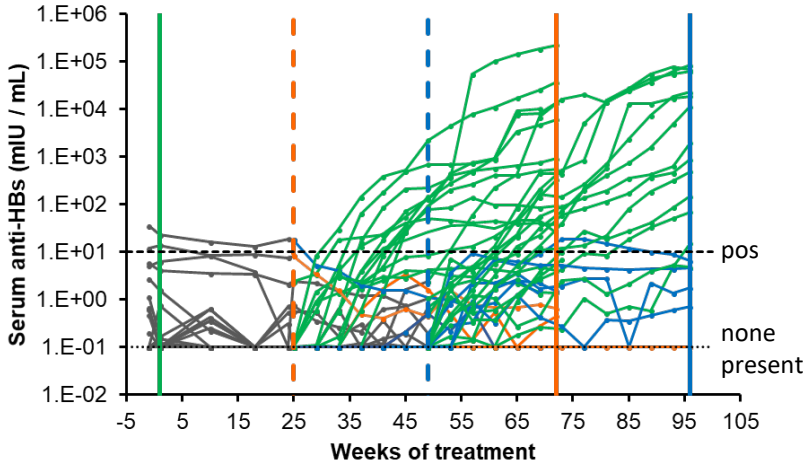
Building a combination regimen with HBsAg loss

Combination effect with TDF and pegIFN

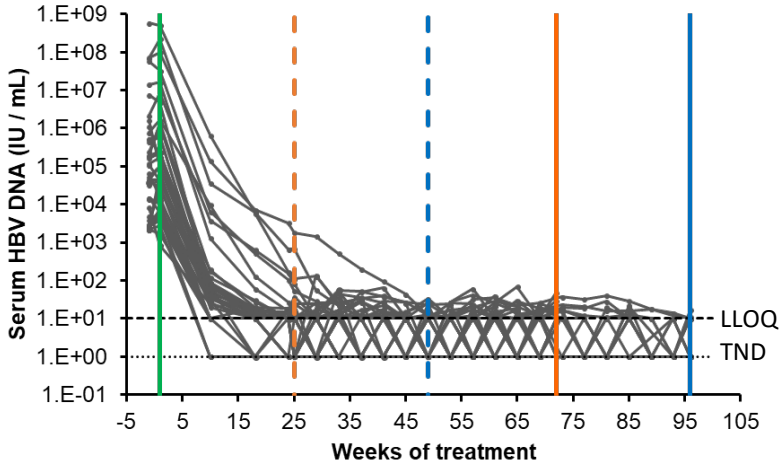
REP 401 study - HBeAg negative chronic HBV mono-infection
40 patients received 48 weeks of REP 2139-Mg or REP 2165-Mg, TDF and pegIFN
Interim analysis from June 1, 2018



REP 2139-Mg = REP 2165-Mg
4/40 non-responders
8/40 HBsAg > 1 log reduction but < 1 IU/mL
28/40 HBsAg < 1 IU/mL
24/40 HBsAg loss (≤ 0.05 IU/mL)



Anti-HBs dramatically increased with the introduction of pegIFN
(but only in patients with HBsAg declines to < 1 IU/mL)



TDF-induced HBV DNA declines unaffected during therapy

Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but < 1 IU/mL | HBsAg < 1 IU/mL

Building a combination regimen with HBsAg loss

Combination effect with TDF and pegIFN

REP 401 study - HBeAg negative chronic HBV mono-infection
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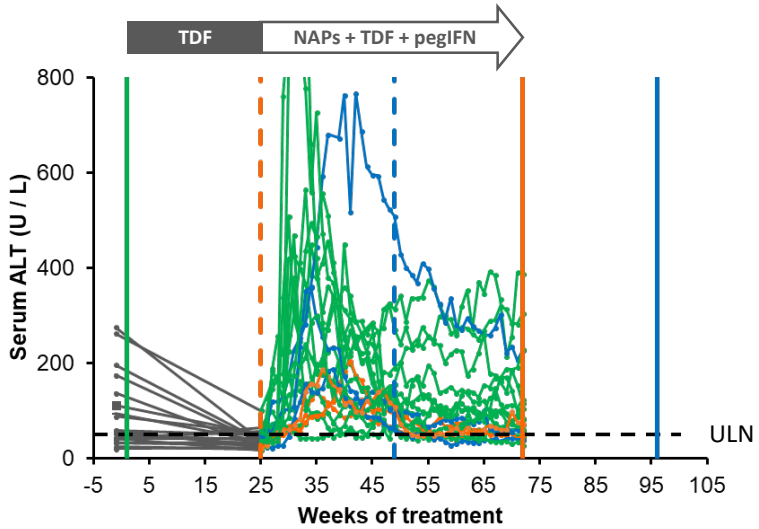

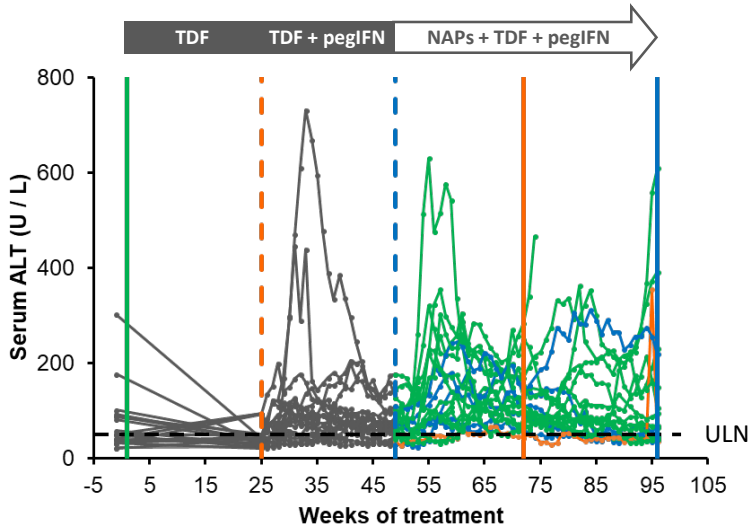

ALT flares observed during immunotherapy
(all otherwise asymptomatic)
(increased intensity in patients with HBsAg declines to < 1 IU/mL)

Flares attenuated when NAPs introduced following 24 weeks of pegIFN

Standard of care only | < 1 log reduction in HBsAg | HBsAg > 1 log reduction but < 1 IU/mL | HBsAg < 1 IU/mL

Building on functional control rates…

Mode	Monotherapy	Combination therapy		
Study	REP 101	REP 102	REP 301	REP 401
NAP	REP 2055	REP 2139-Ca	REP 2139-Ca	REP 2139-Mg REP 2165-Mg
Immunotherapy	none	pegIFN **thymosin alpha 1**	pegIFN	pegIFN **(full course of 48 weeks)**
NUC	none	none	none	TDF
Population	HBeAg positive HBV mono-infection	HBeAg positive HBV mono-infection	HBeAg negative HBV / HDV co-infection	HBeAg negative HBV mono-infection
Number treated	8	12 (9 received combination)	12	40
Follow-up: Functional control HBV DNA < 1000 IU/mL		8/9 initially 4 @ 2 years (HBsAg < 1 IU/mL)		26/30 (87%)*
Follow-up: Functional control HBV DNA < LLOQ	3 @ 1 year 2 @ 5 years (HBsAg = 0.08 and 0.03 IU/mL)		6 HBV DNA < LLOQ @ 2 years 7 HDV RNA TND @ 2 years (4/12 HBsAg ≤ 0.05 IU/mL)	21/30 (70%)* (16/30 HBsAg ≤ 0.05 IU/mL)*

* Patients completing ≥ 24 weeks of follow-up as of June 1, 2018

Summary

Restoration of immune (functional) control of HBV infection can be achieved by HBsAg clearance alone

- But only occurs in a small subset of patients

Antiviral effect of immunotherapy is dramatically improved with HBsAg clearance

- Improved rates of HBsAg decline and profound increases in anti-HBs
- Otherwise asymptomatic (and likely therapeutic) transaminase flares are stronger and more prevalent
- Improved rates of functional control of HBV and HDV infection observed after removal of all therapy
- **pegIFN is easily managed and safe when combined with TDF and REP 2139-Mg or REP 2165-Mg**
- **HBsAg clearance will improve the effects of other immunotherapies targeting HBV infection**

Antiviral response to immunotherapy (even combined with DAAs) is unlikely in the absence of HBsAg reduction

- Consistent with current lack of antiviral response to TLR-agonists and therapeutic vaccines in clinical trials
- Antiviral response to pegIFN is infrequent and only marginally improved when combined with TDF or ETV

TDF also has immunotherapeutic properties and may improve functional control rates (with HBsAg clearance)

- Currently 87%* (HBV DNA < 1000 IU/mL) and 70%* (HBV DNA < LLOQ) when combined with REP 2139-Mg and pegIFN
- Accompanied by normalization of liver function

* Patients completing ≥ 24 weeks of follow-up in the REP 401 protocol as of June 1, 2018

Acknowledgments

A collaborative effort!

Clinical evaluations:

Montreal, Canada
Michel Bazinet

Dhaka, Bangladesh
Mamun Al-Mahtab

Chișinău, Moldova
Victor Pântea
Valentin Cebotarescu
Lilia Cojuhari
Pavlina Jimbei
Gheorghe Placinta
Liviu Iarovoi
Valentina Smesnoi
Tatiana Musteata
Iurie Moscalu
Alina Jucov

Clinical virology and assay validation:

Essen, Germany
Adalbert Krawczyk

Munich, Germany
Michael Roggendorf
Hadi Karimzadeh
Hrvoje Mijočević
Zainab Usman

Los Angeles, USA
Peter Schmid
Jeffrey Albrecht

Bobigny, France
Emmanuel Gordien
Frédéric Le Gal

Pre-clinical evaluations:

Adelaide, Australia
Allison Jilbert
Faseeha Noordeen
Catherine Scougall

Lyon, France
Lucyna Cova
Celia Brikh
Jonathan Quinet
Catherine Jamard

Essen, Germany
Michael Roggendorf
Katrin Schöneweis
Mengji Lu
Pia Roppert
Dieter Glebe

Logan, Utah, USA
John Morrey
Neil Motter

Reno, Nevada, USA
Doug Kornbrust

Mechanistic studies:

Montreal, Canada
Matthieu Blanchet
Patrick Labonté

Paris, France
Camille Sureau
Frauke Beilstein
Matthieu Lemasson

Essen, Germany
Ruth Broering
Catherine Real
Joerg Schlaak

Ness Ziona, Israel
Raphael Mayer
Merav Merom Shamur
Ronny Peri-Naor