Are Immune Modulators Really Needed to Cure HBV infection?

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Disclosures for HLA Janssen

GRANTS
AbbVie, Bristol Myers Squibb, Gilead, Innogenetics, Janssen, Medimmune, Merck, Novartis, Roche

CONSULTANT
AbbVie, Arbutus, Benitec, Bristol Myers Squibb, Eiger Bio, Spring Bank Pharma, Gilead, GSK, Fujirebio, Ionis Pharmaceuticals, Janssen, Medimmune, Merck, Novartis, Roche
Advances in HBV treatment

- 1957: Discovery of interferon
- 1990: Discovery of PMEA
- 1991: Discovery of lamivudine (3TC)
- 1998: Discovery of entecavir
- 1999: Lamivudine (3TC) licensed
- 2001: Discovery of telbivudine
- 2003: Adefovir dipivoxil (PMEA prodrug) licensed
- 2005: Peginterferon alfa-2a licensed
- 2006: Entecavir licensed
- 2007: Telbivudine licensed
- 2008: Tenofovir licensed
- 2017: TAF licensed

Adapted from: ClinicalCareOptions.com

* Specific countries only
What can be considered as a defined cure?

- **Virological cure**
  - elimination of cccDNA
  - lowering or silencing cccDNA
  - Undetectable HBV DNA in serum
  - Off-therapy HBsAg loss

- **Disease cure**
  - No risk of progression to liver failure or HCC
  - Identifiable by clinical parameters, biomarkers or gene signatures
Is HBV Treatment Paradigm Changing?

<table>
<thead>
<tr>
<th>Current PARADIGM</th>
<th>New PARADIGM</th>
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<tbody>
<tr>
<td>• Indefinite Treatment</td>
<td>• Finite treatment duration</td>
</tr>
<tr>
<td>• Poor off-Rx response</td>
<td>• Sustained off-Rx response shift towards endpoint of true immune control &amp; HBsAg seroconversion</td>
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<tr>
<td>• Reduces overall mortality</td>
<td>• No increased risk of mortality and HCC</td>
</tr>
<tr>
<td>• Reduce but does not eliminate the risk of HCC</td>
<td>• New HBV treatments with increased chance of curing disease</td>
</tr>
<tr>
<td>• Potent NAs: suppresses viral replication but cannot cure the disease</td>
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Virology

- Blocking viral replication at multiple steps and elimination of ccc DNA will eventually cure HBV infection: no infected hepatocytes left
- Need assays to detect low level replication below current LOD to determine efficacy
- Intense inhibition of protein and virus production may by itself mount an effective immune response
- Modification of AVT may lead to effective immune response: example stopping NA

Immunology

- Virus integrates in host genome and will always remain present in the hepatocytes (or elsewhere?)
- Proof is the HBV relapse (even HBsAg sero-reversion) during immune suppression
- Effective immune control is most likely delivered by immune modulation agents: example efficacy PEG-IFN
Stopping TDF after long-term viral suppression in HBeAg (-) patients: week 48 interim results

TDF-Stop (n=21)

- HBsAg Log_{10} Reduction:
  - Median 0.28
  - Mean 0.77

TDF-Continue (n=20)

- HBsAg Log_{10} Reduction:
  - Median 0.09
  - Mean 0.11

2/21 (10%) HBsAg loss

No HBsAg loss

*Berg T. et al. J Hepatol 2017*
Viral + Immune Target

- Theoretically an attractive option: agents complementary to each other
- HBV impairs innate and adaptive immune function
  - Viral replication
  - Viral protein production
- Viral inhibition $\rightarrow$ improved immune reactivity
- Immunotherapy:  - Eventual push to tip the balance?
  - Smaller therapeutic window (side effects)
  - Heterogeneous response
Primary endpoint catered to treatment modality and patient group?

- Antiviral Therapy
- Immunomodulatory Therapy
- Combination Therapy

- Treatment naive
- Virally suppressed
# Experimental HBV treatment in naive vs virally suppressed patients

<table>
<thead>
<tr>
<th>Treatment Naive</th>
<th>Suppressed</th>
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<tbody>
<tr>
<td>Younger</td>
<td>Have safe and effective therapy with reduction of HCC and improved survival</td>
</tr>
<tr>
<td>Active Disease</td>
<td>Partial immune restoration may benefit immune modifying therapy</td>
</tr>
<tr>
<td>HBVDNA can be used as a biomarker</td>
<td>Potentially better protection against flares</td>
</tr>
<tr>
<td>No resistance</td>
<td>May have more objections to accept experimental therapy</td>
</tr>
<tr>
<td>May be more likely to accept finite therapy</td>
<td></td>
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</tbody>
</table>
## Approaches to Therapy

### Viral targets - DAA
- Viral entry
- cccDNA formation/transcription/ degradation
- RNA intermediates
- Encapsidation
- DNA replication
- Assembly
- Release

### Immunomodulators
- Innate immune response
  - IFN
  - TLR agonists
  - RIG-I agonists
  - STING
- Adaptive immune response
  - Anti-antagonists (checkpoint inhibitors)
  - Therapeutic Vaccination
Have immune modulators increased response rates thus far?

Antiviral

Immune activator

HBV Functional Cure

Controlled Clinical Data on Different Combination Regimens of Antivirals and Immune Modulators
7 patients had HBsAg seroreversion on or after Week 48 (4 [TDF + PEG 48 wk], 3 [TDF + PEG 16 wk → TDF 32 wk])

- 5/7 had ≤1 week of therapy after HBsAg loss
Strategies to evoke adaptive immune response against HBV in chronically infected patients

Ferrari C, Liver Int 2015
ETV and PEG-IFN (ARES Study)

HBeAg positive study
Multicenter, open-label, randomized controlled trial

Response?*

- Entecavir 0.5 mg daily
  - Pegi-IFN alfa-2a 180μg
  - Follow-up
  - 48  72  96
- Entecavir 0.5 mg daily
  - Follow-up
  - 48  72  96
- Entecavir 0.5 mg daily
  - Follow-up
  - 48  72  96

Response: combined presence of HBeAg loss and HBV DNA level < 200 IU/ml at week 48

Brouwer et al. Hepatology 2015
Sustained Response: ETV Peg-IFN add-on vs. ETV ARES Study

ETV PEG-IFN add-on

- 81% Continue ETV therapy
- 19% Response, Stop Rx
- 79% Sustained Response

ETV monotherapy

- 90% Continue ETV therapy
- 10% Response, Stop Rx
- 75% Sustained Response
- 25% Sustained Response

Response: HBcAg loss, normal serum ALT and HBV DNA <2000 IU/mL

Brouwer et al. Hepatology 2015
What about novel compounds?

Antiviral

Immune activator

HBV Functional Cure
Additive antiviral effect of NVR 3-778 with PegIFN on HBVDNA and HBeAg

Negligible effect on HBsAg

Need data on combination of NVR 3-778 and NUC

Longer-term outcomes including HBeAg seroconversion and HBsAg loss needed
TLR 7 Agonist: Efficacy of GS-9620 in virally suppressed patients with CHB

- **GS-9620**: oral, small-molecule, TLR7 agonist
  - Toll-like receptor 7 (TLR7) is a pattern-recognition receptor located in the endolysosomal compartment of plasmacytoid dendritic cells (pDC) and B cells
  - TLR7 activation results in innate and adaptive immune stimulation

**Phase 2 study**
- 1:3:3:3 randomization (placebo; GS-9620 1, 2, and 4 mg)

**1° Endpoint: HBsAg Decline**

![Graph showing median changes in HBsAg up to Week 24](image)

- **Cohort A**: 4-week treatment
- **Cohort B**: 8-week treatment
- **Cohort C**: 12-week treatment

- HBsAg changes were minimal in all cohorts, with no patients having >0.5 Log10 declines in HBsAg at Week 24 in any GS-9620 arm
- No patients had HBsAg loss; 2 patients had HBeAg loss

- **GS-9620 is safe and well-tolerated**
- Dose-dependent induction of ISGs, but no significant HBsAg decline

*Janssen HL, et al. AASLD 2016*
Therapeutic Vaccine: GS-4774 in combination with TDF in patients with chronic hepatitis B not on antivirals

- GS-4774 is a heat-inactivated, yeast-based T-cell vaccine
  - Recombinant protein containing HBV core, surface, and X proteins
  - Immunogenic in mouse models and healthy volunteers\(^1,2\)
    - In virally suppressed CHB patients, GS-4774 showed modest effect on HBsAg decline\(^3\)
- Phase 2 study

<table>
<thead>
<tr>
<th>SC injection Q4W</th>
<th>Primary endpoint: HBsAg decline</th>
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<tr>
<td>Week 0</td>
<td></td>
</tr>
<tr>
<td>n=27</td>
<td>TDF 300 mg QD</td>
</tr>
<tr>
<td>n=57</td>
<td>GS-4774 2 YU TDF 300 mg QD</td>
</tr>
<tr>
<td>n=56</td>
<td>GS-4774 10 YU TDF 300 mg QD</td>
</tr>
<tr>
<td>n=55</td>
<td>GS-4774 40 YU TDF 300 mg QD</td>
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- GS-4774 + TDF safe and well tolerated
- At Week 24, more patients receiving GS-4774 had \(>0.5 \log_{10} \text{IU/mL} \) decline in HBsAg
- By Week 48, all cohorts had similar proportion of patients with \(>0.5 \log_{10} \) decline in HBsAg
- No indication for this vaccine as monotherapy or in combination with NA currently

1 YU, 107 yeast cells
Janssen HL, et al. AASLD 2016
Blocking PD-1 to reverse HBV T cells exhaustion in a WHV model

- Combination therapy that included ETV, DNA vaccine and anti-PD-L1 antibody
- Combination regimen: enhanced HBV specific T cell activation and more robust and sustained suppression of HBV DNA and HBsAg
- Proof of principle to the efficacy of a combination immune modulation therapy with an anti viral agent

Liu J et al, Plos Pathogens 2014
NA and anti-PD-1 treatment with or without Therapeutic Vaccine in HBeAg-negative CHB

**Strategies to mitigate T-cell exhaustion**
Blockade of programmed cell death protein (PD-1) or its ligand (PD-L1) to rescue HBV-specific T-cell responses

**STUDY DESIGN:** Anti-PD-1 antibody nivolumab 0.1 mg/kg (receptor occupancy) to 3 mg/kg plus GS-4774 in HBeAg-negative, virally suppressed (NUC) patients

Gane E, et al. EASL 2017
NA and anti-PD-1 treatment with or without Therapeutic Vaccine in HBeAg-negative CHB

Week 12 HBsAg change from baseline

Week 24 HBsAg change from baseline

- Single dose anti–PD-1 mAb ± GS-4774 well tolerated
- Modest reduction of HBsAg in all treatment arms

Gane E, et al. EASL 2017
Conclusions

Targeting the virus:
• Therapies targeting HBV directly are effective and will come in many flavors interfering with different steps of replication cycle
• Change in viral load has been shown - in a small minority - to induce functional cure (HBsAg loss) either by long-term NA therapy or by stopping NA

Targeting the immune system:
• TLR/RIG-I agonist, therapeutic vaccination, PD1-PDL1 blocking in development: first clinical results negative or modest
• Narrow therapeutic window and heterogeneous response
• Long way to go with immune modulators

Combination therapy most likely needed!
Are Immune Modulators Really Needed to Cure HBV infection?

- I really do not know.

- Probably yes because we have no functional cure with the approach targeting the virus thus far and I personally doubt whether we ever will.

- Slight problem is that we have not found the right immune modulator thus far and that it will be far from easy to find it.
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Toronto, Canada
June 14-17, 2018

Registration Opening: October 3, 2017
Abstract Submission Opening: October 3, 2017
Abstract Submission Closing: February 12, 2018

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www.globalhepatitissummit2018.com @GlobalHepSummit
Basic Science Invited Speakers

Ralf Bartenschlager  
Thomas Baumert  
Antonio Bertoletti  
Andrea Cox  
Maura Dandri  
Geoff Dusheiko  
Ariel Feldstein  
Carlo Ferrari  
Scott Friedman  
Adam Gehring  
Yujin Hoshida  
Michael Houghton

Gordan Keller  
Georg Lauer  
Wenhui Li  
Anna Lok  
Jane McKeating  
Darius Moradpou  
Alex Ploss  
Barbara Rehrenmann  
Christoph Seeger  
Eui-Cheol Shin  
Camille Sureau  
John Tavis

Robert Thimme  
Lorne Tyrell  
Stephan Urban  
Fabien Zoulim
Clinical Invited Speakers

Marina Berenguer
Henry Chan
Carla Coffin
Adrian Di Bisceglie
Greg Dore
Geoff Dusheiko
Jordan Feld
Ariel Feldstein
Xavier Forns
Graham Foster
Michael Fried
Scott Friedman
Scott Fung
Seng Gee Lim
Jeffery Glenn
Zack Goodman
Theo Heller
Ira Jacobson
Harry Janssen
Pietro Lampertico
Jin Lin Hou
Anna Lok
Rohit Loomba
Michael Manns
Francesco Negro
George Papatheodorides
Keyur Patel
Jean Michel Pawlotsky
Ulrike Protzer
Rajender Reddy
Arun Sanyal
Gonzalo Sapinoschin
Shiv Sarin
Mark Sulkowski
Adriaan Van der Meer
Heiner Wedemeyer
Fabien Zoulim