Management of Hepatitis B: New Treatment Paradigms

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June 2013
Lake Louise

1999
Glacier Park Lodge

Chronic HBV Natural History

Resolution  Stabilization  Compensated  Cirrhosis  HCC  Death
Acute infection  Chronic Hepatitis  Asymptomatic carrier
Decompensation  Transplantation  Death
30–50 years
Natural history of CHB in 2012

Immune tolerance: HBeAg
Immune active: HBeAg or anti-HBe
Immune control: Anti-HBe

HBV DNA log10 IU/ml
HBeAg or anti-HBe
HBsAg log10 IU/ml
ALT (U/L)


Different meanings of HBV DNA and HBsAg in CHB

<table>
<thead>
<tr>
<th>Virology</th>
<th>HBV DNA</th>
<th>HBsAg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Virology</td>
<td>Dane particle</td>
<td>Dane particle and subviral particles</td>
</tr>
<tr>
<td>Natural history</td>
<td>Reduced after HBeAg seroconversion but relapse on immune escape</td>
<td>Very slow reduction over time regardless of HBV DNA levels or disease activity</td>
</tr>
<tr>
<td>Implication</td>
<td>Viral replication</td>
<td>Immune clearance of infected hepatocytes</td>
</tr>
</tbody>
</table>

Guidelines HBV Treatment

<table>
<thead>
<tr>
<th>AASLD 2009</th>
<th>EASL 2012</th>
<th>APASL 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Not preferred</td>
<td>Not preferred</td>
</tr>
<tr>
<td>Adefovir</td>
<td>Not preferred</td>
<td>Not preferred</td>
</tr>
<tr>
<td>Entecavir</td>
<td>First line</td>
<td>First line</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Not preferred</td>
<td>Not preferred</td>
</tr>
<tr>
<td>Tenofovir</td>
<td>First line</td>
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<tr>
<td>PEG-IFN</td>
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</tbody>
</table>

In many regions the cost of anti-CHB therapy poses significant financial burden to patients and to the resource-constrained national healthcare systems. Financial burden of treatment remains unaffordable for most patients because of lack of full or adequate reimbursement for treatment.
HBV Treatment Goals

- **Sustained remission**
  - PEG-IFN
  - Low viremia
  - ALT normalization
  - Immune control, no further need for antiviral drugs

- **Maintained Remission**
  - NA
  - Low viremia
  - ALT normalization
  - No immune control, continued need for antiviral drugs

Nucleos(t)ide Analogs

Improving the long-term health of HBV patients with NA rests on these pillars

- Antiviral potency
- High genetic barrier to resistance
- Favorable safety profile
- Regression of disease
- Improved liver histology

- Fibrosis
- Cirrhosis/HCC

- Uncontrolled viral replication
- Non-inferior treatment
Virology & Serology

- Virological response was estimated by KM analysis in 243 NA-naïve patients.
- Virological response was defined as HBV DNA < 80 IU/mL.

**Entecavir: Virological response in NA-naïve patients**

- Virological response was estimated by KM analysis in 243 NA-naïve patients.
- Virological response was defined as HBV DNA < 80 IU/mL.

**Tenofovir: Efficacy Results at Year 5**

<table>
<thead>
<tr>
<th></th>
<th>HBeAg+ Patients</th>
<th>HBeAg- Patients</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TDF-TDF</td>
<td>ADV-TDF</td>
<td>Overall</td>
</tr>
<tr>
<td><strong>ALT</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalized ALT</td>
<td>0% (7/1103)</td>
<td>85% (931/1090)</td>
<td>82% (1662/1951)</td>
</tr>
<tr>
<td>Mean ± SD (U/L)</td>
<td>42 ± 35</td>
<td>32 ± 15</td>
<td>38 ± 20</td>
</tr>
<tr>
<td><strong>HBV DNA</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 400 copies/ml</td>
<td>64% (103/163)</td>
<td>68% (113/167)</td>
<td>65% (216/330)</td>
</tr>
<tr>
<td>Mean ± SD (U/L)</td>
<td>150 ± 115</td>
<td>150 ± 115</td>
<td>150 ± 110</td>
</tr>
<tr>
<td>&lt; 169 copies/ml</td>
<td>63% (102/162)</td>
<td>65% (101/162)</td>
<td>64% (193/306)</td>
</tr>
<tr>
<td>Mean ± SD (U/L)</td>
<td>28 ± 11</td>
<td>27 ± 9</td>
<td>28 ± 8</td>
</tr>
</tbody>
</table>

Zoutendijk et al. Hepatology 2011

Marcellin et al. Lancet 2013
Resistance rates through 6 years among nucleos(t)ide-naive patients

<table>
<thead>
<tr>
<th>Drug Generation</th>
<th>Year 1 (%)</th>
<th>Year 2 (%)</th>
<th>Year 3 (%)</th>
<th>Year 4 (%)</th>
<th>Year 5 (%)</th>
<th>Year 6 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st LVD*</td>
<td>0%</td>
<td>74%</td>
<td>46%</td>
<td>55%</td>
<td>71%</td>
<td>80%</td>
</tr>
<tr>
<td>2nd ADV*</td>
<td>9%</td>
<td>3%</td>
<td>6%</td>
<td>10%</td>
<td>14%</td>
<td>29%</td>
</tr>
<tr>
<td>3rd TDF*</td>
<td>0%</td>
<td>6%</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
<td>1%</td>
</tr>
<tr>
<td>4th ETV*</td>
<td>0%</td>
<td>1%</td>
<td>1%</td>
<td>2%</td>
<td>1%</td>
<td>1%</td>
</tr>
</tbody>
</table>

§ possibility to switch to Truvada after 72 weeks

Management of HBV Resistance
EASL Guidelines 2012

<table>
<thead>
<tr>
<th>Resistance to:</th>
<th>Suggested management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lamivudine</td>
<td>Switch to tenofovir (or add adefovir*)</td>
</tr>
<tr>
<td>Telbivudine</td>
<td>Switch or add tenofovir (or add adefovir**)</td>
</tr>
<tr>
<td>Entecavir</td>
<td>Switch or add tenofovir (or add adefovir*)</td>
</tr>
</tbody>
</table>
| Adefovir | Lamivudine naïve: switch to entecavir*** or tenofovir
Lamivudine resistant: Switch to tenofovir |
| Tenofovir**** | Switch to entecavir (lamivudine naïve)
Add entecavir (lamivudine resistant) |

* If tenofovir is not available
** May be preferred in patients with high viral loads
*** Tenofovir resistance not yet described
**** Tenofovir resistance not yet described

NA management approaches: tailored regimes for the individual patient

- Antiviral treatment
- Viral load assessment
- Treatment failure
- Check compliance
- Wild type virus
- HBV drug resistant mutant
- Check compliance
- Primary non response
- Switch to more potent drug
- Add-on therapy based on cross-resistance data
Iavarone M

**Entecavir: Partial Virological Response at week 48**

- 1 log IU/mL decline in HBV DNA from baseline but a detectable load at week 48
- Partial virological response considered in retreated HBeAg-positives
- High baseline HBV DNA and HBeAg positivity were the only independent risk factors for PVR

Zoutendijk et al. Hepatology 2011

**“Roadmap” concept**

- In principle a good treatment paradigm

However:
- In particular designed for antivirals with suboptimal response and high rate of resistance
- Should not justify to start with the first generation drugs (Lamivudine, Adefovir, Telbivudine)
- Still 6-9% resistance for Telbivudine in patients with undetectable HBV DNA (<300 copies/mL) after 24 weeks
- Requires frequent and expensive HBV DNA testing
- May increase the already existing problem of incompliance
- Long-term safety and cost effectiveness of combination therapy not well established

**Histology**

A small slender core of tissue is removed with a biopsy needle
Tenofovir reduces fibrosis in the majority of patients after 5 years (N=348)

- 96% of patients either improved (≥ 1 unit decrease in fibrosis score) or did not change at Year 5.
- 71/96 (74%) cirrhotic patients and had regression of fibrosis (Ishak score ≤ 4).

Change in Ishak fibrosis scores at year 5 for patients with cirrhosis at baseline

- 96 patients with cirrhosis had paired BL and Year 5 biopsies.
- At Year 5, 74% (71/96) had cirrhosis reversed (Ishak fibrosis score ≤ 5), 73% (70/96) had decreases of 2 or more points; 29% (n=27) did not change.
- Of 34 patients who did not add FTC, 73% had cirrhosis reversed; 26% showed no change.

Prevention of Liver Failure and HCC
Virological response during ETV not influenced by severity of liver disease

- Median follow up 20 months
- 372 CHB patients
- 49% HBeAg+
- Stratified for severity of liver disease at baseline
- Virological response: HBV DNA <80 IU/mL


Virological response to ETV associated with a lower probability of disease progression

- Clinical event defined as development of hepatic decompensation, HCC, or death
- All patients started within the group without VR and were switched when VR was achieved


Long-term ETV treatment reduces HCC incidence in cirrhotic patients

- 472 ETV treated (3.2 yr follow-up) vs 1143 untreated historical controls
- HCC incidence: ETV 2.54% vs control 12.6%

Adapted from Hosaka. Hepatology 2013 in press
Long-term ETV treatment does not reduce HCC incidence in non-cirrhotic patients

Cumulative development rates of HCC (%)

Adapted from Hosaka, Hepatology 2013 in press

ETV treatment reduces liver-related and all-cause mortality in cirrhotic patients

Cumulative probability of all cause mortality

Adapted from Wong, Hepatology 2013

Patient characteristics influence NA treatment complexity

Adherance

Co-morbidities

Gender

Obesity

Imunosuppression

Alcohol

Lifestyle

Family history

Smoking

Diabetes

HCV

HBV

Age

Co-infection

Race

Adherence

Co-morbidities

Gender

Obesity

Imunosuppression

Alcohol

Lifestyle

Family history

Smoking

Diabetes
Key considerations in long-term management: safety

- The risks of adverse events must be balanced versus the benefits before initiating treatment
- The long-term safety of nucleos(t)ide-analogues remains to be determined
- All HBV nucleos(t)ides are generally well tolerated with low rates of discontinuation, but individual safety profiles differ (e.g. renal impairment, myopathy, myalgia)

Can treatment with NA be stopped?

- New cells
- Nucleoside analogs

Current Guidelines about NA Cessation

<table>
<thead>
<tr>
<th></th>
<th>AASLD 2009</th>
<th>APASL 2012</th>
<th>EASL 2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg-positive patients</td>
<td>6 months HBeAg seroconversion &amp; undetectable HBV DNA</td>
<td>6 months HBeAg seroconversion &amp; undetectable HBV DNA</td>
<td>12 months HBeAg seroconversion</td>
</tr>
<tr>
<td>HBeAg-negative patients</td>
<td>HBeAg seroclearance</td>
<td>12 months undetectable HBV DNA</td>
<td>-</td>
</tr>
</tbody>
</table>

Sustained remission of disease is not achieved in a majority of patients with HBeAg seroconversion during NA therapy.

Continuation of therapy until HBsAg seroconversion appears necessary.

HBeAg negative and HBV DNA <10,000 copies/mL after HBeAg seroconversion.

Reijnders et al. Gastroenterology 2010

HBeAg and HBVDNA recurrence in NA therapy: lack of immune control?

- Recurrence is likely to occur when the suppressive effect of nucleos(t)ide analogues is omitted, whether by discontinuation of therapy or by development of antiviral drug resistance.
  - On-treatment recurrence primarily in lamivudine-treated patients due to resistance.
  - Off-treatment recurrence in all nucleos(t)ide analogues, irrespective of consolidation therapy.

- Long-term continuation of nucleos(t)ide analogue therapy might be necessary, irrespective of the occurrence of HBeAg seroconversion.

Reijnders et al. Gastroenterology 2010

HBsAg decline in patients treated with ETV or TDF: need for host immune response

- Patients treated with ETV or TDF who achieved a Viral Response (VR).
- No difference in HBsAg decline between treatment regimens.

Reijnders et al. J Inf Dis 2011
Potential predictors of outcome after NUCs cessation

Independent predictors of virological relapse:

<table>
<thead>
<tr>
<th>Predictor</th>
<th>HR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAM resistance</td>
<td>3.630</td>
<td>1.781 – 7.482</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time to undetectable HBV DNA during treatment</td>
<td>1.293</td>
<td>1.083 – 1.542</td>
<td>0.004</td>
</tr>
<tr>
<td>HBsAg level at end-of-therapy</td>
<td>1.007</td>
<td>1.001 – 1.012</td>
<td>0.015</td>
</tr>
</tbody>
</table>

1 - Liang et al. AP&T 2011; 2 - Chan et al. Antiviral Ther. 2011

Can therapy with NAs be stopped?

- Long-term viral suppression is achieved
- Off-therapy response unclear – limited sustained immune control
- Increasingly common question encountered in the clinic is ‘when can therapy be stopped?’
- Monitoring HBsAg may help us identify patients who can stop NAs with a low chance of relapse

(Pegylated) Alpha-Interferon
Why is finite therapy a goal for treatment?

- Younger patients may find lifelong treatment hard to accept
- Women who want to become pregnant
- Patients reluctant to start treatment
- Cost savings to healthcare system
- Long-term adherence issues
- Working days lost to hospital visits

HBeAg (+) patients: More HBsAg decline with PEG-IFN than ETV

Response to PEG-IFN 6 months post treatment
3-year follow up of HBeAg responders to PEG-IFNα-2b: HBeAg-positive CHB

Percentage initial responders (%)

- HBeAg negative
- HBV DNA >10,000 copies/ml
- HBV DNA <1000 copies/ml
- ALT normal
- HBeAg negative overall

81% 69% 46% 70% 50%

n=64 n=172

Buster et al. Gastroenterology 2008

IFNα-2b Treatment is Associated with Prolonged Survival

Proportion of patients surviving

Cirrhosis at baseline

No cirrhosis at baseline

Years

Years

0.0 0.2 0.4 0.6 0.8 1.0

0.0 0.2 0.4 0.6 0.8 1.0

Responders Non-responders

v Zonneveld et al. Hepatology 2004

Indivdualised Therapy

Large global studies on PEG-IFN therapy show sustained off-treatment response in approximately one third of the patients

Which patients belong to this one third?

Individualised therapy in HBV infection
Response to PEG-IFN in HBeAg positive CHB

PEG-IFN α-2b - HBeAg Loss ¹

PEG-IFN α-2b - HBsAg Loss ²


PEG-IFN induced HBsAg decline varies by HBV genotype (n=803)

PEG-IFN Therapy

Candidates for PEG-IFN Therapy in HBeAg positive CHB (n=808)

HBV genotype

PEG-IFN in case of ALT > 2 ULN OR HBV DNA>10⁶

PEG-IFN in case of ALT > 2 ULN AND HBV DNA<10⁶

Generally not good candidates for PEG-IFN

Sonneveld et al. Hepatology 2013 in press

Buster et al. Gastroenterology 2010; www.liver-gi.nl

high ALT > 2 ULN; low HBVDNA < 10e9 copies/ml
Wildtype, PC and BCP mutants in HBeAg positives according to HBV Genotype (n=263)

Genotype A (n=74)
- Wildtype: 24%
- Precore: 6%
- Basal core promoter: 7%
- Both mutants: 45%

Genotype B (n=19)
- Wildtype: 69%
- Precore: 31%

Genotype C (n=29)
- Wildtype: 24%
- Precore: 7%
- Basal core promoter: 45%

Genotype D (n=85)
- Wildtype: 41%
- Precore: 41%
- Basal core promoter: 18%
- Both mutants: 2%

Sonneveld et al. Hepatology 2012

Influence of the presence of precore and core promoter mutants on response to PEG-IFN

Week 78 (n=263)

<table>
<thead>
<tr>
<th>Response</th>
<th>Wildtype</th>
<th>Non-Wildtype (PC / BCP mutants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBeAg loss</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Combined response</td>
<td>34</td>
<td>3</td>
</tr>
<tr>
<td>HBV DNA &lt;80 IU/mL</td>
<td>21</td>
<td>10</td>
</tr>
<tr>
<td>HBeAg loss</td>
<td>10</td>
<td>4</td>
</tr>
</tbody>
</table>

P<0.001

Sonneveld et al. Hepatology 2012

Combined response: HBeAg loss and HBV DNA<80 IU/mL

Role of the IL28B in control of chronic HBV infection with PEG-IFN?

- In chronic hepatitis C, strong association between SNP in IL28B gene and response to PEG-IFN + RBV
  - Patients with the favorable IL28B genotype were >2x more likely to respond to 48 weeks of treatment
- Mechanism not well understood
- However, IL28B is likely to influence the innate antiviral immune response

Is there an association between IL 28B polymorphism and response to PEG-IFN in CHB?


Sonneveld et al. Hepatology 2012

Combined response: HBeAg loss and HBV DNA<80 IU/mL
IL28B is associated with PEG-IFN induced HBeAg & HBsAg response

305 consecutive HBeAg-positive patients at 11 European and Asian hospitals treated with PEG-IFN

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When to start PEG-IFN in CHB?

Summary

<table>
<thead>
<tr>
<th>Peginterferon</th>
<th>HBV genotype</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A&gt;B&gt;C&gt;D</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HBV DNA</th>
<th>≤10^9 copies/mL</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>ALT</th>
<th>ALT &gt;2 x ULN</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Viral Genome</th>
<th>Wildtype vs PC/BCP</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Severity of liver disease</th>
<th>Compensated</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Age</th>
<th>Younger</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>IL-28 B Genotype?</th>
<th>AA or CC</th>
</tr>
</thead>
</table>

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Two concepts for response-guided therapy approach based on HBsAg levels in PEG-IFN

- Identify responders (PPV)
- Identify non-responders (NPV)

- Continue therapy
- Change strategy
- Motivate the patient
- Stop PEG-IFN (or add on an NA?)
- Track success
- The earlier the better

Time points, cut-off levels may differ?
HBeAg positive CHB: PEG-IFN α-2b Responders achieve a strong HBsAg decline

Mean change in HBsAg (log IU/mL)

Non-response (N=145)

HBeAg response (N=145)*

Combined response (N=42)**

Non-response

Combined response

Week 12:
- HBeAg-positive
  - HBsAg <1500 IU/mL
  - >10% decline in HBsAg?
  (Week 24 for geno D)
- HBeAg-negative
  - No decline in HBsAg or HBsAg >20,000 IU/mL
  - <2log decline HBV DNA

Week 12:
- HBeAg-positive
  - No decline in HBsAg or HBsAg >20,000 IU/mL
  - <2log decline HBV DNA
- HBeAg-negative

Practical application of response-guided therapy using HBsAg levels in PEG-IFN

Sonneveld et al. Hepatology 2013 in press
Effect of ETV +/- TDF in NA-naïve patients

- Number of patients: HBV DNA <50 IU/mL (% patients)
  - All HBeAg + BL HBV DNA <10^8 IU/mL: 111
  - All HBeAg + BL HBV DNA ≥10^8 IU/mL: 138
  - All HBeAg -: 122

- ETV: 80.4%
- ETV+TDF: 83.0%

Difference: 2.6% (95% CI 0.0, 5.2)

Loh A F et al. Gastroenterology 2012

PEG-IFN α-2b vs PEG-IFN α-2b + Lam

- HBeAg loss
- PEG-IFN (n=136): 29%
- PEG-IFN + Lam (n=130): 44%

52 weeks end of therapy
62 weeks end of follow-up

P=0.01
P=0.91

Janssen et al. Lancet 2005

PEG-IFN α-2b vs PEG-IFN α-2b + Lam

HBV DNA Levels

Janssen et al., Lancet 2005
ETV and PEG-IFN (ARES Study)

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

Response? *

<table>
<thead>
<tr>
<th>Week</th>
<th>Peg-IFN α1b in HBeAg</th>
<th>Entecavir 0.5 mg daily</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
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</tbody>
</table>

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

Sonneveld et al. AASLD 2012

ETV and PEG-IFN Combination increases HBsAg decline and clearance of HBeAg

Results: Current week 48.

- HBeAg clearance: P=0.07
- HBsAg decline: P<0.001

By June, 2012, there are 161 patients when 48-week treatment end and others will complete the therapy in 2 months.

Sonneveld et al. AASLD 2012

New Treatments for HBV
Towards new HBV treatment targets

New HBV targets

Additional therapeutic strategies aiming at inhibiting different steps of the HBV life-cycle or mediating host factors are needed and at early stages of development:

- PEG-IFN Lambda
- TLR agonists
- Cyclophilin inhibitors
- HBsAg release inhibitors
- Entry inhibitors
- Therapeutic vaccination

Peginterferon Lambda for CHB: Comparison with Peg-IFN Alfa in HBeAg positives

HBV DNA decline

HBsAg decline

Chan NL et al. AASLD 2012
Peginterferon Lambda for CHB: Comparison with Peg-IFN Alfa in HBeAg positives

<table>
<thead>
<tr>
<th>Patients n (%)</th>
<th>Lambda 180 μg N = 80</th>
<th>Alfa 180 μg N = 83</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluctuant symptoms</td>
<td>11 (14)</td>
<td>39 (47)</td>
</tr>
<tr>
<td>Constitutional symptoms</td>
<td>23 (29)</td>
<td>23 (28)</td>
</tr>
<tr>
<td>Neurologic</td>
<td>16 (20)</td>
<td>30 (36)</td>
</tr>
<tr>
<td>Musculoskeletal symptoms</td>
<td>7 (9)</td>
<td>26 (31)</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>7 (9)</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Dose reductions due to AE</td>
<td>6 (8)</td>
<td>21 (25)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>0</td>
<td>12 (15)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

Chan NL et al. AASLD 2012

GS-9620: Oral TLR-7 Agonist

- TLR-7
  - Intracellular pathogen sensor
  - endolysosomal RNA
  - Agonism induces anti-viral response via innate immune activation
- GS-9620
  - Oral
  - Nanomolar potency
  - Selective (TLR-7 >>> TLR-8)
  - Pharmacodynamic effects in mouse, woodchuck, cyno, chimp, human

GS-9620: Reduction in HBV DNA, and Serum HBsAg and HBeAg in Chimpanzee

Lanford et al. Gastroenterology 2013 in press
**Tarmogen: Therapeutic Vaccination**

- Tarmogens are made from genetically modified yeast that express one or more disease-associated antigens.
- Activate T cells to specifically target and eliminate diseased cells with the same target antigen.
- Safe and well tolerated:
  - >300 subjects treated for up to 4 years
- HBV-specific Tarmogen
- Scalable, efficient manufacturing

**Myrcludex B: Acylated HBV preS1-derived peptides block HBV infection in vitro**

- Entry inhibitor
- Chemically synthesized lipopeptides derived from the envelope of HBV block virus infection in cell culture (HepaRG & PHH)
- Administration of Myrcludex B prevents the establishment of de novo HBV infection in vivo

Petersen, Dandri et al. Nature Biotech. 2008
Functional Receptor for HBV Discovered (NTCP)

- Scientists from National Institute of Biological Sciences (NIBS), Beijing discovered a functional receptor for Hepatitis B virus (HBV) infection
  - It opens doors for future high throughput drug screen
  - as well as revealed an important new target for treating HBV infection and related diseases

Inhibition of HBV infection the receptor-binding region of pre-S1 specifically interacts with sodium taurocholate cotransporting polypeptide (NTCP), a multiple transmembrane transporter predominantly expressed in the liver.


Conclusions I
Nucleos(t)ide Analogues

- Major improvement in HBV therapy in the last decade
- Good virological response with very limited resistance for potent last generation NA
- Profound improvement in inflammation & fibrosis
- Reduction of liver failure and most probably also of HCC and all cause mortality
- Side effects limited but further monitoring warranted
- HBeAg seroconversion is suboptimal endpoint for NA
- NA therapy is most probably indefinite in vast majority of patients

Conclusions II
Immune Modulation

- Try to aim for sustained off-treatment response
- PEG-IFN in selected proportion of patients: based on HBV genotype, wildtype, HBVDNA, ALT, and IL28B?
- Response Guided therapy based on HBsAg is there
- Promising results PEG-IFN combined with potent NA
- New agents which may induce immune control over HBV are coming!
Future Perspectives

- Shift towards endpoint of HBsAg seroconversion
- Combination of the most potent nucleos(t)ide: Peg-IFN add on therapy?
- Further tailored therapy according to host genetics
- Wider indication for HBV therapy?
- More development of new drugs which will induce immune control over HBV!