Pipeline and new strategies for HBV treatment

Maurizia Rossana Brunetto

Dipartimento di Medicina Clinica e Sperimentale - Università di Pisa

UO Epatologia – Azienda Ospedaliero Universitaria Pisana - Centro Riferimento Regionale “Diagnosi e trattamento delle epatopatie croniche e del tumore di fegato”
Disclosures

**Advisory board:** AbbVie, Gilead, Roche

**Speakers’ bureau:** AbbVie, BMS, Gilead, MSD, Janssen

**Research grant:** AbbVie, BMS, MSD
New nomenclature: based on the description of the 2 main characteristics of chronicity, infection vs hepatitis.
Cure vs Control

Liver disease

Cure: resolution of the chronic liver disease

Control: halting progression of the disease, without complete resolution, but with reduction/elimination of the complications

 HBV infection

Cure: clearance of the viral infection or complete shut-down of cccDNA

Control: achievement of an effective inhibition of viral replication, usually on therapy
Chronic Hepatitis B: from cure of the disease to its control

- **Portal**
  - S 0-1

- **Periportal**
  - S 2-3

- **Septal**
  - S 2-4

- **Inc. cirrhosis**
  - S 3-5

- **Comp. Cirrhosis S**
  - 4-6

Images and diagrams illustrate various stages of liver damage and progression from portal to periportal to septal stages, with incipient and complete cirrhosis.

1-6 yrs → 5-15 yrs → 5-15 yrs → 1-6 yrs
Regression of cirrhosis during treatment with TDF for CHB: a 5 year open label follow-up study

- Of 641 patients who received randomized treatment, 585 entered the open label phase and 489 (76%) completed 240 weeks: **348 pts (54%) had liver biopsy at BL and 240 w.**
- **87%** (304) of the pts had **histological improvement** and **51%** (176) regression of fibrosis at w 240.

**Change in Ishak score in 96 cirrhotics**

- BMI, history of diabetes, abnormal ALT and Knodell score >3 were associated with persistence of cirrhosis at 5 y.
The PAGE B cohort study: 10-year cumulative probability of HCC during NUC therapy

After the first 5 years of ETV or TDF therapy in CHB patients, the HCC incidence is decreasing, with the decrease being more evident in patients with baseline cirrhosis.

Papatheodoridis G et al, Hepatology 2017
Eight-year survival in CHB patients under long-term ETV and TDF therapy is similar to the general population

1951 adult Caucasian with CHB with (27%) /without cirrhosis, without HCC at BL on NUCs for at least 12 months /median 6 years

Survival probability at

<table>
<thead>
<tr>
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<th>1 y.</th>
<th>3 y.</th>
<th>5 y.</th>
<th>8 y.</th>
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</thead>
<tbody>
<tr>
<td>CHB without CI</td>
<td>100</td>
<td>98.5</td>
<td>97.3</td>
<td>96.2</td>
</tr>
<tr>
<td>CHB with CI</td>
<td>99.1</td>
<td>95.9</td>
<td>92.8</td>
<td>89.3</td>
</tr>
</tbody>
</table>

- Mortality of non-cirrhotics seems to be lower than that of the general population
- Mortality of cirrhotics is similar to that of the general population
- HCC is the main factor affecting patient mortality
- 2.6% of the patients had major liver-related events events (death or OLT)

Overall mortality rate was 0.77 (95%CI 0.62-0.96) comparable to that of the general population, 0.82 (95%CI 0.66-1.039)

Papatheodoridis G et al, J Hep 2018
Response to antiviral treatment: how it is changing the way to look at it

Virological responses
- **during NA** undetectable HBV DNA by a sensitive PCR (LoD 10 IU/ml)
- **after NA**, sustained off-therapy virological response, HBV DNA <2,000 IU/ml for at least 12 months
- **during PegIFNa** HBV DNA <2,000 IU/ml at 6 months and at the end of therapy.
- **after PegIFNa** HBV DNA <2,000 IU/ml for at least 12 months

Serological responses
- **HBeAg** are HBeAg loss and HBeAg seroconversion
- **HBsAg** are HBsAg loss and HBsAg seroconversion

Complete sterilising cure:
undetectable serum HBsAg and eradication of HBV-DNA including intrahepatic cccDNA and integrated HBV-DNA

Functional cure:
sustained, undetectable serum HBsAg and HBV-DNA with/without seroconversion to anti-HBs (several levels of functional cure according to cccDNA status: complete shut down of cccDNA transcription or its elimination)

Partial cure:
detectable serum HBsAg, but persistently undetectable serum HBV-DNA
Why to cure HBV infection?

- To achieve a persistent control of HBV infection off therapy in a higher proportion of cases
- To achieve a complete inhibition of HBV replication
- To halt events that may have oncogenetic potential
- To increase the therapeutic index of antiviral treatment
- To increase the number of patients who could have cured their chronic hepatitis B
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Partial cure: detectable serum HBsAg, but **persistently undetectable** serum HBV-DNA

On or off therapy

EASL, HBV CPG 2017

Lok A et al, J Hep 2018
Successful antiviral treatment in CHB patients

Hepatitis resolution after relapse

Brunetto MR et al, Hepatology 1989
Phase 1 studies with new drugs for the treatment of CHB

HBV capsid assembly modulator, JNJ-56136379

RNA interference (RNAi), ARO-HBV

Phase 1 studies are mainly aimed to test:
➢ Safety
➢ Tolerability
➢ Pharmacokinetics
➢ Antiviral activity

Zoulim F, et al. AASLD 2018, San Francisco, USA. #74
Gane E, et al. AASLD 2018, San Francisco, USA. #LB-25
REP 2139-Mg / REP 2165-Mg, TDF and pegIFNα-2a in patients with HBeAg negative CHB

- 40 patients
- 5 with advanced fibrosis (according to Fibroscan values)

*CROSSED over at 24 wks due to poor HBsAg response (< 3 log reduction in HBsAg)

ALT profile

38/40 pts had ALT flare concomitantly with REP's exposure
ALT flare?  

bad

good

At present the definition is only based on the ex post evidence of

**Good, beneficial, therapeutic flares**
- when they are associated with the achievement of the control of the infection
- because asymptomatic
- because self-limited
- because not associated with liver dysfunction

**Virologic response**

**Absence of clinically relevant events**

However, *a priori* the flare remains always potentially threatening in a patient with advanced fibrosis and reliable predictive factors are missing
Control or Cure of HBV infection for a personalized treatment

Type of drugs’ combination according to:

✓ Virus and infecting viral population
✓ Phase of HBV infection
✓ Stage of liver disease
✓ Treatment status (naive or on treatment)
✓ Host features (age, gender, co-morbidities)

HBV cure vs HBV infection control

Liver disease control
Antifibrotic, antiangiogenetic drugs
Future HBV therapies: new targets, new drugs

Immunomodulation
- **Innate Immunity**
  - Toll-like receptors agonists (7 and 8)
  - RIG-1 Agonist
- **Adaptive Immunity**
  - Anti-PD-1 mAb, TCR engineering
  - Vaccine therapy

RNA interference, (siRNA) e.g. ARC-520, ARO-1001, ARB1467, ARB-270729

Inhibition of HBsAg release (NAPs), e.g. REP 2139, REP 2165

Polymerase inhibitors
- Nucleoside analogues, e.g.
  - TAF, amdoxovir, MIV-210
- Non-nucleoside, e.g. LB80380

Capsid Assembly Modulators, e.g. Bay 41-4109, RO7049389, JNJ-6379, NVR1221, AB-506

Entry inhibitors (HBV/HDV)
- Lipopeptides, e.g. Myrcludex-B

Targeting cccDNA
- HAPs
- Chromatin-modifying enzymes

HBV Direct Antivirals: Targeting cccDNA

**Strategies targeting the cccDNA:**
- cccDNA formation
- eliminating existing cccDNA
- silencing cccDNA transcription

Nassal et al, Gut 2015
Targeting HBc protein / HBV capsid by Core inhibitors / Core Protein Assembly Modulators (CpAM)

- Capsid formation and pgRNA encapsidation pivotal for infective particles production
- HBc binds the cccDNA and modifies cccDNA nucleosome spacing

Capsid Assembly Modulators (CpAM):
- **class 1 CpAM** (RO7049389) induces aberrant core protein aggregates, that are subsequently degradated
- **class 2 CpAM** (JNJ-6379) block pgRNA encapsidation with production of empty capsids
RO7049389, a core protein allosteric modulator (CpAM), is effective against HBV, safe and well tolerated

RO7049389 is an oral small molecule, Class I HBV CpAM

Methods:
YP39364 is a Phase I study investigating safety, PK and anti-viral activity of RO7049389
- SAD and MAD cohorts in healthy volunteers have been completed
- Dosing in the first patient cohort at 200mg bid for 28 days is complete

Results:
➢ To date, RO7049389 is well tolerated with no clinically significant changes or trends evident in safety data
➢ Robust HBV DNA declines: median (maximal) –2.7 (–3.4) log_{10} IU/ml, observed to Day 28 of dosing 200 mg bid (n=6)
➢ Future cohorts will explore higher doses and once daily dosing

*HBV DNA Values <LLOQ and below the lower limit of detection

Gane E, et al. ILC 2018, #LBO-003
Safety, PK and antiviral activity of a novel HBV capsid assembly modulator, JNJ-56136379, in patients with CHB

**JNJ-6379** is a CAM that binds to HBV core protein and disrupts early and late-stage processes in the HBV lifecycle.

**“Primary” mechanism (“empty capsid” CAM)**
Interference with capsid assembly kinetics, preventing encapsidation of (pg)RNA and blocking HBV replication (late step in viral life cycle) - **JNJ-6379 median EC$_{50}$/EC$_{90}$ = 102/376 nM**

**“Secondary” mechanism**
Inhibition of de-novo formation of cccDNA, potentially by interfering with capsid disassembly process (early stage in viral life cycle) - **JNJ-6379 median EC$_{50}$/EC$_{90}$ = 876/4019 nM**

- HBeAg +ve or –ve
- Non-cirrhotics (F0–F2)
- Plasma HBV DNA >2000 IU/mL
- ALT <2.5 x ULN
Safety, PK and antiviral activity of a novel HBV capsid assembly modulator, JNJ-56136379, in patients with CHB

- **Change in HBV DNA**

  **On treatment**

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>BL Mean (SD)</th>
<th>Mean (SD) change from BL</th>
<th>Patients with HBV DNA &lt;LLQ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>5.59 (2.37)</td>
<td>2.30 (0.59)</td>
<td>3 (38)</td>
</tr>
<tr>
<td>75</td>
<td>3.39 (2.21)</td>
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<td>0.02 (1.10)</td>
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- **After treatment**

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<th>Dose (mg)</th>
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- **Dose-related suppression of viral replication, majority of high-dose patients became HBV DNA <LLQ**
- **No reduction in HBsAg but treatment duration short**
- **One on-treatment Grade 4 ALT elevation**
Poor innate immune response with limited quantity of cytokines (IFN-α, IL-6, TNF-α) 

HBV specific T-cell dysfunction, due to persistent exposure to high Antigen doses, T-reg suppression, Dendritic cell impairment
Inhibition of HBsAg production

- Mean nadir HBsAg ranging from -39% to -51% with a mean change on day 85 of 31-22%.
- This is the first time that a reduction in HBsAg mediated through RNA interference has been shown in chronic HBV patients.

- REP 9-AC HBsAg serum clearance in 7/8 HBeAg+ pts with durable HBV-DNA reduction in 2/7 responders.
- REP 2139 monotherapy, followed by combination with Peg-IFN and Peg-IFN monotherapy led to undetectable HDV-RNA in 10/12 HDV pts, without rebound of HBsAg in pts with levels < 10 IU/ml.

RNAi-Based Treatment of Chronically Infected Patients and Chimpanzees Implicates Integrated Hepatitis B Virus DNA as a Source of HBsAg

- **siRNA in ARC-520 was designed to target all HBV mRNAs**

- **ARC-520 reduced** significantly serum HBsAg and HBeAg in HBeAg positive naive pts, but not in HBeAg negative pts or HBeAg pos on prolonged NUC treatment

**Quantification of liver HBV-DNA in ARC-520 treated chimps**

- **ARC-520 was not active mRNAs from integrated HBV-DNA**

  - Studies in chimps suggest a dramatic increase of the integration in the HBeAg negative phase.
  - >90% of the mRNAs deriving from integrated HBV-DNA
  - A significant proportion of HBsAg in HBeAg negative patients could derive from integrated HBV sequences

Wooddell C et al  Sci Transl Med 2017
First results with RNA interference (RNAi) in CHB using ARO-HBV

AROHBV1001 background

- ARC520/521 RNAi program demonstrated need to target integrated HBs in HBeAg–ve CHB patients
- Membrane lipid protein delivery - endos required IV administration, associated with preclinical toxicity
- ARO-HBV is new TRiM™ delivery system for RNAi

- X and S triggers → silence all mRNA from both cccDNA and host integrated viral DNA
- GAL-NAC conjugation allows SC administration

AROHBV1001 study design

- SAD in 6 cohorts of healthy volunteers (4 active: 2 PBO) received 35, 100, 200, 300, 400 mg
- MAD in 6 cohorts of CHB patients (4, open-label) received ARO-B 100, 200, 300, 400 mg Q4W x3
  - Cohorts 2b–5b HBeAg +/-ve NUC-naive or suppressed
  - Cohort 8 HBeAg pos naive (start NUC on Day 1)
  - Cohort 9 HBeAg+ve suppressed
- Endpoints: PK, safety and tolerability of ARO-HBV
  - HBsAg reduction from baseline in CHB patients

- ARO-HBV well tolerated at single or multiple monthly SC doses up to 400 mg
- Robust HBsAg decline in all HBV patients (1.3–3.8 log_{10}) – slower than with IV ARC-520/521
- No clear dose-response above 100 mg
- HBsAg declines similar in HBeAg +ve and HBeAg –ve
- Associated DNA, RNA, HBeAg, HBcrAg responses
High rates of functional control and reversal of fibrosis following treatment of HBeAg negative chronic HBV infection with REP 2139-Mg / REP 2165-Mg, TDF and pegIFNα-2a

- ALT flares were observed in 38/40 patients concomitantly with REP 2139-Mg / REP 2165-Mg exposure.
- ALT flares were self-resolving, otherwise asymptomatic and correlated with reductions in serum HBsAg during treatment.
- 44% of the patients at 24-48 post-treatment follow-up show the HBeAg negative infection profile and 41% a functional cure.
- REP 2139-Mg/REP 2165-Mg are effective and well tolerated in combination with pegIFN and TDF in HBeAg neg. CHB and elicit the establishment of functional control of HBV infection persisting after removal of therapy.
- To avoid unspecific boosting of innate immunity
- To tailor the HBV specific immunity limiting the killing of infected hepatocytes

Adapted from Bertoletti A et al, Curr Op Infect Dis 2014
TLR7 agonist RO7020531 + CpAM RO7049389 achieved sustainable VL suppression and HBsAg loss in an AAV-HBV mouse model

*Combination of RO7049389 and RO7020531 reduced HBsAg level to below LLOQ at the end of treatment in 5 of 7 animals, reduced HBV DNA level to below LLOQ in all animals, which sustained in 4 of 7 during 6-week off-treatment follow-up.
Inarigivir (SB 9200) demonstrates potent dose dependent antiviral activity in HBV naive patients: Role of HBeAg status and BL HBsAg in antiviral response

INARIGIVIR: a RIG-I agonist with a dual mechanism
- Restores hepatic selective innate and adaptive immune response stimulating the production of type I and III IFNs
- Inhibits HBV replication complex via direct acting antiviral effect

Dose response in both HBeAg negative and HBeAg positive patients at Wk 12

HBeAg negative

<table>
<thead>
<tr>
<th>Inarigivir dose</th>
<th>HBV DNA</th>
<th>HBV RNA</th>
</tr>
</thead>
<tbody>
<tr>
<td>25 mg</td>
<td><img src="image1.png" alt="Graph" /></td>
<td><img src="image2.png" alt="Graph" /></td>
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<tr>
<td>50 mg</td>
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</tr>
<tr>
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</tr>
<tr>
<td>Placebo</td>
<td><img src="image7.png" alt="Graph" /></td>
<td><img src="image8.png" alt="Graph" /></td>
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</table>

Inarigivir dose

Inarigivir 25 mg

12 weeks monotherapy QD

≤80 non-cirrhotic HBV patients, randomized 4:1

≤80 non-cirrhotic HBV patients, randomized 4:1

12 weeks monotherapy QD

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12 weeks monotherapy QD

≤80 non-cirrhotic HBV patients, randomized 4:1

60 CHB patients:
- 11 pts PBO
- 33 HBeAg pos
- 16 HBeAg neg

Yuen MF, et al. AASLD 2018, San Francisco, USA. #75
Inarigivir (SB 9200) demonstrates potent dose dependent antiviral activity in HBV naïve patients: Role of HBeAg status and BL HBsAg in antiviral response

HBV RNA reduction after switching to TDF in patients on inarigivir but not PBO

- HBsAg reduction of 0.8 $\log_{10}$ (range 0.5–1.4) in 13 responder pts (>0.5 log reduction in HBsAg)
- HBsAg response associated with declines in HBV DNA and HBV RNA
- BL HBsAg <4 logs, BL IP-10 and Wk 12 IP-10 decline predicted HBV DNA and HBV RNA responses
- ALT flares >200 IU/mL in 6 pts on inarigivir (associated with HBV DNA and RNA reduction in 4 wks) and 3 pts on PBO; no changes in bilirubin, INR or with flares

➢ Dose-response in HBV RNA and HBsAg reduction with inarigivir
➢ Effect more prominent in HBeAg –ve than HBeAg +ve pts
➢ ALT flare may indicate immune clearance induced by inarigivir
Unmet need for a personalized management of current and future antiviral treatments

- Identification of the immunological profile associated with an effective control of HBV infection

- Availability of biomarkers with high diagnostic accuracy in the identification of the carriers who achieved an effective and persistent control of HBV infection
Hepatology Unit
University Hospital of Pisa, Italy

Medical Doctors
Barbara Coco
Piero Colombatto
Filippo Oliveri
Veronica Romagnoli
Antonio Salvati
Gabriele Ricco
Lidia Surace
Riccardo Gattai

Administrative Personnel
Arianna Del Chicca

Biologists
Daniela Cavallone
Francesco Moriconi
Pierpaola Tannorella

Bio-Physics
Luigi Civitano
Ranieri Bizzarri

Nurses
Antonella Cristofani
Simonetta Ferretti (part-time)
Simona Giannetti
Teresa Crisponi
Barbara Zucchelli
Raffaele Apuzzo

INNOVATIVE MODEL OF PERSONALIZED CARE
Ferruccio Bonino
UPMC Institute for Health Chianciano